ORPHAN DRUGS BECOME BILLION DOLLAR BABIES

1983 Orphan Drug Act Swells Pharma’s Coffers ............... 12

Little Orphan Handy Guide
Just the Facts of the Debate .......... 18

Venture Philanthropy
Straddles Two Worlds .................... 22

www.managedcaremag.com
Healthsense makes it easier to manage the costs of Managed Care.

Small changes in the daily activity of seniors can signal health concerns. Healthsense uses unique remote monitoring technology to collect and analyze this information and initiate action to help you ensure a higher quality of care, with a reduced total expense.

With Healthsense, customers have seen up to a $687 reduction in healthcare costs per member per month.

- **67% REDUCTION** in long term care costs
- **32% REDUCTION** in acute hospitalizations
- **29% REDUCTION** in ER fees

See what we can do for you. Contact us directly so we can tailor the right connected health solution for your organization at [healthsense.com/managedcare](http://healthsense.com/managedcare)

Healthcare cost reduction realized through 12-month matched cohort study comparing claims and survey data between a study group and a historical control group. Enrolled members saw an average $687 PMPM cost reduction, including a 67% reduction in long-term care costs, a 32% reduction in acute hospitalizations and a 29% reduction in ED fees. Financial savings may vary by organization and are not guaranteed. Copyright ©2017 GreatCall, Inc.
M

ANaged Care publishes original papers and feature articles dealing with diverse elements of the health care system. Among these are impartial peer-reviewed research and review articles examining clinical and financial aspects of managed care.

ALAN G. ADLER, MD
Senior Medical Director
Independence Blue Cross

PARTHSA ANBIL
Principal
The ConfluenceElite Group LLC
West Chester, Pa.

JAN BERGER, MD, MJ
President
Health Intelligence Partners
Chicago, Ill.

THOMAS BODENHEIMER, MD
Family and Community Medicine
University of California–San Francisco
San Francisco, Calif.

PETER BOLAND, PhD
President, Boland Healthcare
Berkeley, Calif.

LARRY S. BORESS, MPA
President & CEO
Midwest Business Group on Health
Chicago, Ill.

H. ERIC CANNON, PharmD
Chief of Pharmacy
SelectHealth/Intermountain Healthcare
Salt Lake City, Utah

GEORGANNE CHAPIN, MPhil, JD
President & CEO
Hudson Health Plan
Tarrytown, N.Y.

VIVIAN H. COATES, MBA
Vice President
Information Services and Health Technology Assessment
ECRI Institute
Plymouth Meeting, Pa.

HELEN DARLING
Strategic Adviser
Former President and CEO
National Business Group on Health
Washington, D.C.

GARY SCOTT DAVIS, JD
Partner, Health Law Department
McDermott, Will & Emery LLP
Miami, Fla.

D.S. (PETE) FULLERTON, PhD, RPh
Strategic Pharmacy Innovations
Seattle, Wash.

ARCHELLE GEORGIOU, MD
Founder
Georjou Consulting
Minneapolis, Minn.

JEFF GOLDSMITH, PhD
President, Health Futures Inc.
Charlottesville, Va.

ALICE G. GOSFIELD, Esq.
Principal, Gosfield & Associates

MICHAEli T. HALPERN, MD, PhD
Associate Professor of Public Health
College of Public Health
University of Arizona
Tucson, Ariz.

JAN HIRSCH, PhD
Associate Professor of Clinical Pharmacy, Scaggs School of Pharmacy and Pharmaceutical Sciences
University of California–San Diego
San Diego, Calif.

GEORGE J. ISHAM, MD
Senior Adviser
HealthPartners
Minneapolis, Minn.

LUCY JOHNS, MPH
Independent Consultant
Health Care Planning and Policy
San Francisco, Calif.

ROBERT C. JOHNSON, MS
President, R.C. Johnson & Associates
Former President, American Pharmaceutical Association
Scottsdale, Ariz.

THOMAS KAYE, RPh, MBA
Pharmacy Consultant
Louisville, Ky.

RANDALL KRAKAUER, MD, FACP, FACR
Vice President, National Medical Director,
Medical Strategy
Aetna
Princeton, N.J.

PETER KONGSTVEDT, MD, FACP
President
P.R. Kongstvedt Co.
McLean, Va.

THOMAS H. LEE, MD, SM
Chief Medical Officer
Press Ganey Associates
Wakefield, Mass.

ATEEV MEHROTRA, MD, MPH
Associate Professor of Medicine and Health Care Policy
Department of Health Care Policy
Harvard Medical School
Boston, Mass.

MICHAEL L. MILLENSON
President
Health Quality Advisors LLC
Highland Park, Ill.

THOMAS MORROW, MD
Chief Medical Officer
Next IT
Spokane, Wash.

SAM NUSSBAUM, MD
Executive Vice President and Chief Medical Officer
Anthem
Indianapolis, Ind.

MATT NYE, PharmD
Vice President
Pharmacy Care Support Services
Kaiser Permanente
Downey, Calif.

BURTON I. ORLAND, BS, RPh
President
BioCare Consultants
Westport, Conn.

STEVEN R. PESKIN, MD, MBA, FACP
Associate Clinical Professor of Medicine
University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School
New Brunswick, N.J.

UWE E. REINHARDT, PhD
James Madison Professor of Political Economy
Princeton University
Princeton, N.J.

EMAD RIZK, MD
President & CEO
Accretive Health
Chicago, Ill.

JOHN ROGLIERI, MD, MBA
Medical Director
New York Life Insurance Co.
New York, N.Y.

TIM SAWYERS, BPharm, MBA, PAHM
Director of Account Management
Magellan Rx Management
Nashville, Tenn.

JAMES M. SCHIBANOFF, MD
Editor-in-Chief, Milliman Care Guidelines
Milliman USA
San Diego, Calif.

STEPHEN W. SCHONDELMEYER, PharmD, PhD
Professor & Director, PRIME Institute
University of Minnesota College of Pharmacy
Minneapolis, Minn.

JAAN SIDOROV, MD, MHSA
Chief Medical Officer
medSolis
Frisco, Texas

THOMAS D. SNOOK, FSA, MAaa
Principal & Consulting Actuary
Milliman Inc.
Phoenix, Ariz.

RICHARD G. STEFANACCI, DO, MGH, MBA, AGSF, CMD
Chief Medical Officer, The Access Group
Jefferson College of Population Health
Thomas Jefferson University

F. RANDY VOGENBERG, PhD, RPh
Partner
Access Market Intelligence
Greenville, S.C.

JONATHAN P. WEINER, DrPH
Professor and Director of the Center for Population Health
Johns Hopkins University
Bloomberg School of Public Health
Baltimore, Md.
‘That needs to stop’

By Peter Wehrwein

When Kaiser Health News published its investigation of orphan drugs in January, it shed light on a troubling corner of the pharmaceutical market.

The Orphan Drug Act is now 34 years old, and it has accomplished what it set out to do—and then some. The economics of developing treatments for rare diseases were unworkable. Now they are veritable gold mines for pharmaceutical companies.

EndPoint News published its “10 most expensive drugs on the planet” list in April, and every one of them was, no surprise, an orphan drug. Topping the tally is Horizon Pharma’s Ravicti with a wholesale acquisition cost of $793,632. The company disputes that figure. BioMarin’s Brineura was second on the list, coming in at $702,000, although according to Bloomberg, BioMarin also says that price is unrealistic and that after mandatory government discounts (most of the patients are on Medicaid) the price will be $486,000.

(Yep, we definitely need some price transparency.)

High drug prices for truly rare diseases do present a dilemma. Private companies need a return on investment. The markets and the patients—infants and children—are often tiny. But high prices are one thing. These astronomical ones, another.

Besides, as Kaiser and Contributing Editor Joseph Burns reports in this issue (page 12), the intent of the orphan drug law is being undermined. Drugs approved as orphans now rack up blockbuster sales as they accrue multiple indications and are used off label. Common diseases are “salami sliced” by biomarker into rare ones so the drugs to treat them can gain orphan status and the attendant benefits (subsidies, market exclusivity, etc.). “That needs to stop,” David Mitchell told Burns. Mitchell is the founder of a new—and much-needed—group, Patients for Affordable Drugs.

Mitchell’s right. It is time to tighten up the Orphan Drug Approval so its original good intentions are realized, not taken advantage of.

Clinical judgment must guide each clinician in weighing the benefits of treatment against the risk of toxicity. Dosages, indications, and methods of use for products referred to in this publication may reflect the professional literature or other clinical sources, or may reflect the clinical experience of the authors, and might not be the same as what is on the approved package insert. Please consult the complete prescribing information for any products mentioned in this publication. MMMM Group LLC assumes no liability for the information published herein.

Copyright 2017 by MMMM Group LLC. All rights reserved under the United States, International, and Pan-American copyright conventions. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, photocopying, electronic, or otherwise, without the prior written permission of MMMM Group LLC. The copyright law of the United States governs the making of photocopies or other reproductions of copyrighted material.

Subscriptions for individuals or institutions in the U.S.A. are $70 per year, $10 per single copy; elsewhere, $120 per year, $22 per single copy. Inquiries about paid subscriptions: Dawn Flook, telephone (267) 685-3422; email: dflook@medimedia.com.

Postmaster: Send address changes to Managed Care, PO Box 2019, Morrisville, PA 19067. Periodicals postage paid at Morrisville, Pa., and at additional mailing offices.
**Orphan Drugs: Handle With Care**

**Orphans Swell Drug Spending**

The Orphan Drug Act of 1983 is one of the best things to happen to drug companies. Predictions have annual worldwide sales climbing into the billions. Insurers are just beginning to push back.  
*By Joseph Burns*

**A Cheat Sheet for the Orphan Drug Debate**

Yes, the 1983 Orphan Drug Act succeeded. But high prices and allegations that some drug companies have twisted the law to their advantage abound. The main arguments are laid out.  
*By Krishna R. Patel*

**These Orphans Aren’t Poor**

Sales of orphan drugs are forecast to grow 11% over the next five years, to $209 billion. That’s twice as fast as the expected increase in the sales of all other prescription drugs.  
*By Ed Silverman*

**Venture Philanthropy Straddles Two Worlds**

One expert argues that it’s a little like calling someone an amateur-pro athlete. You can’t be both. Proponents, however, point to some initially impressive results especially for niche diseases.  
*By Howard Wolinsky*

**Care Coordination (Isn’t)**

The health system has embraced the process in a big way. Perhaps in too big a way because hospitals, insurers, drug companies ... you name it. They all have their ideas. The result? Too often it’s confusion.  
*By Jan Greene*

**Original Research**

**Slow Down the Transitional Revolving Door**

A program developed to address problems in post-acute transitional care seems to be effective in reducing 30-day readmission rates for some Medicare fee-for-service beneficiaries.
Death Rate for Older Black Americans Continues Declining This Century

The mortality gap between white and black America still exists, but it’s getting smaller. In fact, black Americans who reach age 65 are now expected to live longer than white Americans of the same age, according to a study by the CDC that looks at death rates for the 21st century.

The study found that among adults ages 65 and older, the death rate in 2015 relative to that in 1999 declined 27% for blacks and 17% for whites. In 2010, the death rates crossed over; blacks in that age group had lower death rates than whites.

While both black and white Americans are living longer, the death rate for blacks has been dropping faster than for whites. At the beginning of the century, the life expectancy for black Americans at birth was 71.8 years; it was 77.3 years for whites.

Now, black Americans have a life expectancy of 75.6; for whites, it’s 79 years. Go back to 1999, and look at the trend to 2015 and you’ll see that the death rate for blacks declined by 25%.

Heart disease, the leading cause of death in the United States, kills blacks and whites at about the same rate, according to the CDC. However, blacks who are younger than 65 die more often from chronic diseases such as diabetes and stroke.

“Of concern, the study also found that blacks in their 20s, 30s, and 40s are more likely to live with or die from conditions that typically occur at older ages in whites...,” according to the CDC. “Risk factors for some diseases, such as high blood pressure, may go unnoticed and untreated during these early years.”

The biggest gap can be found in the homicide rate. For blacks ages 18 to 34, it is nine times higher than for whites. For blacks ages 35 to 49, it is five times higher than for whites. As the CDC notes, “the death rates for homicide among blacks did not change over the 17 years of the study.”

Leandris Liburd, the associate director of the CDC’s Office of Minority Health and Health Equity, said in a statement: “We have seen some remarkable improvements in death rates for the black population in these past 17 years. Important gaps are narrowing due to improvements in the health of the black population overall. However, we still have a long way to go. Early health interventions can lead to longer, healthier lives. In particular, diagnosing and treating the leading diseases that cause death at earlier stages is an important step for saving lives.”

How socioeconomic factors affect health should be taken into consideration, according of the CDC. “In all age groups, the analysis showed that blacks had lower educational attainment and home ownership and nearly twice the rate of poverty and unemployment as whites. These risk factors may limit blacks’ access to prevention and treatment of disease. Other risk factors that affect health outcomes for blacks include obesity and less physical activity.”

Board Removes Molina Brothers
CEO J. Mario Molina, and his brother, CFO John Molina, were fired by the Molina Healthcare’s board of directors. The announcement, made May 2, cited the company’s disappointing financial performance, according to FierceHealthcare. The Molina brothers are the sons of the company’s founder, C. David Molina.

J. Mario Molina was one of the health insurance industry’s biggest supporters of Obamacare and the company, which focuses on Medicaid managed care, seemed to be doing better under the ACA than competitors.

The 4 million-member company was expected to rake in $16 billion in revenue by the end of 2016. “The thing that surprised us is that we actually exceeded our growth expectations,” J. Mario Molina told The Hill in September 2016.
That was then. In February of this year, Molina Healthcare showed a net loss of $47 million in the fourth quarter of 2016 compared with a $30 million profit in the fourth quarter of 2015.

J. Mario Molina, 58, who assumed the CEO mantle in 1996 after his father’s death, told Kaiser Health News that the reversal was due to what he saw as a structural flaw in the ACA known as risk transfer. It’s one of the subsidies accorded insurance companies who wind up losing money for serving a sicker, poorer population. Except this subsidy doesn’t come from the government directly but from other insurers who don’t have as many sicker, poorer patients.

J. Mario Molina said that he liked the idea but said the formula used to carry it out was flawed. It punished efficiency rather than helped companies that have had some bad luck in the risk pool.

“Let’s put it this way,” he told Kaiser. “Currently, Molina Healthcare is returning 25% of our premiums to the government, which are then distributed to our competitors. So we are really subsidizing our competitors and helping them, rather than forcing them to compete.”

**CMS Wants More Hospital Transparency**

The Joint Commission conducts surprise inspections of hospitals at least once every 39 months. Just what the commission finds, however, is rarely disclosed to the public, according to ProPublica, a not-for-profit news gathering organization. In fact, the commission makes the 4,018 hospitals on its list sound almost too good to be true: 99% have full accreditation.

Are hospitals really that good? The only way to find out is to make the inspections by the private accreditors public knowledge. That’s what would happen under what ProPublica describes as a “groundbreaking” proposal by CMS, which would require detailed public reports by the accreditors. The proposal would also require the hospitals to disclose how it is fixing the problems. (The Joint Commission told ProPublica that it is still reviewing the CMS proposal.)

Right now, critics argue, the commission offers very little feedback on what it finds. As ProPublica reports: “For one hospital, the explanation is: ‘Existence at time of survey of a condition, which in the Joint Commission’s view, poses a threat to patients or other individuals served.’ The threat itself is not disclosed.”

Officials with the Healthcare Facilities Accreditation Program, another private accreditor, wonder just what it would take to make the proposal work in the real world. What staff would be needed and at what cost? “It’s hard not to support the goals, but we have to look at the execution,” Gary Ley, the executive director, told ProPublica.

The American Hospital Association also has some reservations. Nancy Foster, AHA’s vice president of quality and patient safety, said in a statement: “It’s important that the information shared with consumers has a clear purpose, is transparent, and is readily understood by folks from all walks of life, not just those with deep expertise in health care. We are concerned that sharing a detailed report may not be the most useful or effective strategy for informing the public.”

She favors giving the public a one- or two-page summary of the findings that could show it “how the hospital plans to address the findings.”

CMS is taking comments on the proposal until June 13.

**Express Scripts, Anthem May Split Up**

There’s a sliver of hope that the 10-year contract between the nation’s biggest PBM and one of the biggest health insurance companies might yet be salvaged. Bloomberg News reported that Anthem’s CEO Joseph R. Swedish said last month: “We’ve not made a final decision with respect to any vendor. We’ve not ruled anyone in or out. I think that covers the entire spectrum of vendor possibilities, and I’ll leave it at that.”

There’s certainly some bad blood, as Anthem last year sued Express Scripts for $15 billion, claiming that the PBM overcharged the insurer. A third of Express Scripts’ profits before taxes last year (or $2.25 billion) came from Anthem. The insurer accounted for 18% of Express Scripts’ business in the first quarter of this year.

This on-again, off-again relationship has certainly played havoc with Express Scripts’ stock. On April 25,
How physicians will fare under MACRA

A recent study in *Health Affairs* projects physician payment rates under MACRA, comparing them to what they would have looked like had MACRA not been passed. Researchers with Rand compared the two MACRA payment tracks that physicians will be able to choose from starting in 2019: the Merit-Based Incentive Payment System (MIPS), and the advanced alternative payment models (APMs). The two will replace the "widely reviled" Sustainable Growth Rate formula, which was intended to limit growth in Medicare spending. Instead, Congress overrode those cuts 17 times between 2003 and 2015 because the planned increases would have been so small that they might have forced many doctors to not accept Medicare patients.

Physicians who participate in MIPS would be eligible to receive plus or minus 4% reimbursement in 2019 and will possibly go up to 9% in 2022; bonuses for top performers may be increased by a factor of up to 3 until 2024. Physicians who are a part of an APM are qualified for a 5% incentive payment.

By 2030, payment rates are expected to be 8% higher for physicians in the MACRA APM track. They're expected to be 5% higher for physicians in the MIPS track, the study states.

Keep an eye on what happens in 2025, a pivotal year, according to the Rand experts, "one in which a confluence of policy factors are expected to significantly reduce physician payments, a situation reminiscent of the SGR." Beginning in 2025, doctor payment rates in both the APM and MIPS tracks will fall below the projected pre-MACRA baseline.

Projected Medicare physician payment rates under MACRA vs. a pre-MACRA baseline scenario, 2015–2030

Physician payment rate relative to 2015

- Pre-MACRA baseline
- MACRA APM track
- MACRA MIPS track

Source: Hussey PS et al., *Health Affairs*, April 2017
older, the focus might be heart disease and other chronic conditions.

Patient volume differs depending on the location. “Typically, we see 25 to 80 patients a day in our emergency departments,” Richard Bonnin, the communications director for Emerus, tells the magazine. Emerus operates more than 20 microhospitals across the country. “Of those who receive inpatient care, the average length of stay is two days.”

Health Benefits Top Employee Wish List

Eighty-seven percent of workers consider employer-sponsored health benefits to be important or extremely important when it comes to maintaining or looking for a job, according to a study by the Employee Benefit Research Institute (EBRI). That tops the list of what benefits employees like most about a job, with a retirement savings plan coming in second (77%), and a dental or vision plan third (72%).

That’s what workers want, but many feel they’re not getting it. Thirty-two percent say they are only somewhat satisfied with their benefits; another 20% are not satisfied, according to the study.

And here’s an alert for companies about morale: Only about half (49%) are extremely or somewhat confident that their employer will continue to offer a similar benefits package three years from now.

In addition, the study states that nearly 6 in 10 workers (59%) who are extremely satisfied with their benefits are also extremely satisfied with their job overall (compared with 18% who are very satisfied with their benefits or just 8% who are not satisfied with their benefits).”

Paul Fronstin, director of EBRI’s Health Research and Education Program and co-author of the new report, tells Plansponsor, a publication that reports on the retirement benefits industry, that “employers that offer a strong employee benefits package—especially health coverage—that balances costs and choice should find themselves with a competitive advantage over other companies when it comes to attracting and retaining desirable workers. They also will have more satisfied employees overall.”

Forty-six percent of workers who get benefits through their employers paid less than $2,500 on those benefits, according to the EBRI report; 18% paid between $2,500 and $4,999; and 14% paid $5,000 or more.

“These amounts may be more than some can afford: 1 in 10 (10%) say they reduced or discontinued some other employee benefits in the past year in order to pay for health insurance,” the study states.

Then, there are the employees who are not sure just what benefits they have. Thirty-three percent don’t know if their employer offers health insurance for early retirees; 30%, home health insurance; 30%, supplemental health insurance for retirees; and 26%, supplemental health for workers.

“Even when workers know that the benefits are offered, sizable shares (ranging from one in 10 to just over two in 10) do not know whether their employer contributes to the cost of the coverage or whether it is a voluntary employee-paid benefit,” the study states.

Briefly Noted

Use of statins to reduce the risk of having a second heart attack is recommended, but adherence is a problem, according to a study published in JAMA Cardiology. Researchers at the Icahn School of Medicine at Mt. Sinai looked at data on nearly 30,000 Medicare patients who had a high-intensity statin prescription (40–80 mg of atorvastatin or 20–40 mg of rosuvastatin) within 30 days of discharge. Most (58.9%) stuck with the regimen for six months. But two years out, only 41.6% of patients were taking the statins as directed, and many were taking lower doses than they should have been taking.…. The fate of the ACA is nothing if not uncertain, but ACOs may survive—even thrive—regardless of what happens to Obamacare. An ACO coordinated by Anthem and Aurora Health Care helps Burlington Graphics in Racine, Wis., offer a comprehensive approach to wellness for its employees, according to the Journal Times of Racine. “One piece of the population health services at Burlington Graphics is access to an onsite nurse who is at the company’s headquarters a few times per month, helping employees manage their chronic conditions and navigate health care needs,” the newspaper reports.….. People with a diet high in cholesterol do not have a higher risk of dementia or Alzheimer’s disease, according to a Finnish study published in the American Journal of Clinical Nutrition. Indeed, “moderate egg intake may have a beneficial association with certain areas of cognitive performance,” the authors concluded….. Taking away the fear of prosecution encourages people with substance abuse problems to seek help. That’s one of the lessons of a program called Safe Station, which is being credited with reducing overdose fatalities in Nashua, N.H., by 34% and saving $2 million in emergency department care, reports HealthIT Analytics. The program set up services for people with substance abuse problems at seven fire stations in the city.….. Many states have a very narrow legal definition of insanity, reports Stateline (published by the Pew Charitable Trusts). One result is that people with severe mental illness who commit a crime often face the death penalty. Legislators in at least seven states — Arkansas, Indiana, Ohio, South Dakota, Tennessee, Texas and Virginia—have proposed bills this year to prohibit the death penalty for people who suffered from a serious mental illness at the time of their crime, Stateline reports.

— Frank Diamond

ADVERTISING INDEX

GLAXOSMITHKLINE
Viv------------------------ Cover 4

GREATCALL INC.
Healthsense---------------- Cover 2

WALGREENS
Health Solutions--------------- 15
The Heavy Hitters in the Senate As Repeal and Replace Moves On

Now it’s the Senate’s turn. The key players include Republican senators from states that expanded Medicaid and the upper chamber’s parliamentarian.

By Richard Mark Kirkner, Contributing Editor

When the deciding vote was cast in the House to pass the American Health Care Act, Democrats in the chamber started singing “Na Na Na Na Hey Hey, Goodbye” to razz their Republican colleagues about their midterm election prospects. But even before Democrats sang their last goodbye, Republican leaders in the Senate had already decided they would call their own tune on health care.

What helped get the American Health Care Act over the finish line was an amendment crafted by Rep. Tom MacArthur, a New Jersey Republican, himself the subject of a contentious town hall meeting a week after the vote. MacArthur’s amendment loaded the House bill with state waivers from key ACA provisions like prohibiting insurers from charging higher premiums for pre-existing conditions and requiring coverage of certain essential health benefits. But how many states will want to take advantage of the waivers in the House bill and jump into getting involved in the vexatious nongroup health insurance market?

Not many, predicts Joseph Antos, a scholar at the conservative American Enterprise Institute, but the particulars of the House bill might give them pause. “I think states are very interested in waivers,” Antos says. “I just don’t think they’re going to be very interested in what was set up in the MacArthur amendment.”

When Wisconsin Gov. Scott Walker, a Republican, said he might be willing to seek a waiver to let insurers charge higher premiums for people with pre-existing conditions, his counterpart in Connecticut, Dannel Malloy, who is chair of the Democratic Governors’ Association, quipped, “He should run on that.”

Starting from scratch

But eventually, the MacArthur amendment may fall by the wayside or be significantly rewritten.

“The House bill is not going to come before us,” Sen. Susan Collins, a moderate Republican from Maine, has said. “The Senate is starting from scratch.”

Sen. John Cornyn, the Senate majority whip who is also a member of the Senate Health Care Working Group, may have been purposely vague when he told the Hill that the health care bill would be finished before year’s end. But the controversy surrounding President Trump’s firing of FBI Director James Comey could derail efforts to craft new health care legislation—and just about everything else.

But presuming that it does go ahead, here are some of the people who are expected to play a major role in the shaping of the Senate’s health care bill:

Parliamentarian Elizabeth MacDonough. Perhaps overlooked by some, but MacDonough—not a senator but a lawyer who has held the position since 2012—determines what legislation complies with the Byrd rule, named for the late West Virginia Sen. Robert Byrd. The Byrd rule requires that legislation must only affect spending and revenue to qualify for reconciliation and a mere majority vote. Otherwise, it needs 60 votes and is subject to filibuster.

How MacDonough would rule on a Senate bill is anyone’s guess. In 2015, when the House sent over ACA-repeal legislation that would have killed the Independent Payment Advisory Board, MacDonough determined the bill did not meet the Byrd rule, effectively killing it because the Republicans did not have a filibuster-proof majority.

How far could the Senate bill go and still stay in the budget reconciliation/Byrd rule lane? Republican Sen. Mike Lee of Utah, a member of the Senate Working Group on Health Care, told the Washington Examiner that MacDonough told him that legislation could dig into the provisions that affect the private insurance market. “What
I understood her to be saying is that there’s no reason why an Obamacare repeal bill necessarily could not have provisions repealing the health insurance regulations,” Lee told the newspaper.

But if certain pieces of the House bill make it into the Senate version, Antos isn’t so sure they would meet the reconciliation test. “I don’t think any of the insurance market changes in the House bill can make it through the Byrd rule,” he says. “[That includes the age-rating markup moving from three-to-one to five-to-one, but it also includes the MacArthur amendment.”

At least in the early going, MacDonough’s calls as the parliamentary umpire could be crucial to the outcome of any Senate legislation. After all, even getting to 51 votes may not be something Republicans can do on their own. Planned Parenthood advocates could bail out over funding. Twenty Republican senators represent states that expanded Medicaid and getting every one of those votes could hinge on saving that program. Conservatives could balk at funding either one, which would make the votes of Democrats all the more important.

**The Senate Health Care Working Group.**

This all-male, all-Republican group of 13 has been working on the Senate bill. Members include Majority Leader Mitch McConnell of Kentucky. It’s skewed to three conservative states with two members from each—Texas, Wyoming, and Utah. None of those states voted to expand Medicaid, from which the House bill would cut $880 billion over the next 10 years. But McConnell and four other members—Rob Portman of Ohio, Tom Cotton of Arkansas, Cory Gardner of Colorado, and Pat Toomey of Pennsylvania—are from Medicaid expansion states.

Cornyn, who is from Texas, told the *Washington Post* that the health care working group was designed by McConnell to be a smaller group of people that represent the different perspectives and points of view in the Republican conference. “If that group can get to ‘Yes,’ then [we will] take it to the rest of the conference,” Cornyn told the newspaper.

**Sens. Collins and Bill Cassidy of Louisiana.**

This duo introduced ACA repeal-and-replace legislation of their own, the Patient Freedom Act, back in January. Their bill would repeal the ACA’s individual and employer mandates but keep popular provisions like pre-existing condition coverage and allowing children up to age 26 to stay on their parents’ plans. It also preserves mental health and substance abuse coverage. Cassidy seems to understand that public opinion, amp’d up by social media, matters. He appeared on Jimmy Kimmel’s show last month and discussed “the Jimmy Kimmel test,” a reference to the late-night TV host’s tearful monologue about his infant son’s congenital heart defect and keeping health care affordable.

Collins has taken issue with several aspects of the House bill. For example, the tax credits to buy health insurance in the AHCA range from $2,000 to $4,000 annually and are based on age. Collins has said other factors need to be taken into account: “One of the problems with the House bill is that the tax credits are not adjusted for income or geographic region,” she said. “That really hurts a state like Maine where we have an older population living in largely more expensive rural areas.” She has also criticized the AHCA for giving states too much leeway in setting insurance rules.

“The difference between [the AHCA] approach and the approach in the bill that Sen. Cassidy and I have introduced is that we keep the ACA safeguards, the consumer protections for people with pre-existing conditions,” Collins said last month on one of the Sunday morning political chat shows.

**GOP Planned Parenthood supporters.**

Collins and Alaska Sen. Lisa Murkowski have both said they would not support defunding of Planned Parenthood, which the House legislation does.

**Other Republican senators from states that expanded Medicaid.** This group includes Murkowski; Cassidy; Shelley Moore Capito of West Virginia, where one fourth of the population is on Medicaid; Dean Heller of Nevada, and Jeff Flake of Arizona. The latter two are up for election next year and are considered vulnerable.

**A couple of Democrats.** Minority Leader Chuck Schumer of New York will play a significant role just by virtue of his position as leader of the Democratic opposition.

Sen. Joe Manchin of West Virginia is another key Democrat because his state has so much riding on Medicaid. Manchin also is up for election next year and has a primary challenger, so don’t look for him to support legislation that would mean deep Medicaid cuts.

**“The House bill is not going to come before us,” says Sen. Susan Collins of Maine. “The Senate is starting from scratch.”**
Cardiovascular disease is perhaps the most dangerous consequence of diabetes, despite the ravaging impact that neuropathy, nephropathy, and retinopathy can have on people with the disease. About two out of three people ages 65 or older with diabetes die from heart disease, and about one in seven die from stroke. Put another way, adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes.

The link between diabetes and cardiovascular disease has been clear for decades, but until 2015 no clinical trial had convincingly demonstrated a link between medications that lower blood glucose and cardiovascular risks. Then the EMPA–REG OUTCOME trial reported data that showed that empagliflozin, sold as Jardiance, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, reduced cardiovascular deaths by an impressive 38%. Based on those results, the FDA added a new indication for Jardiance in December 2016, which made it the first drug approved to reduce cardiovascular mortality in people with type 2 diabetes.

Since then, a growing number of companies have applied for similar cardiovascular indications for their diabetes drugs. A race is on between the SGLT2 inhibitors like Jardiance and the glucagon-like peptide 1 (GLP-1) agonists like liraglutide, sold as Victoza, and dulaglutide, sold as Trulicity, to see which can generate the most convincing cardiovascular results and win FDA approval.

An equally important scramble among drug manufacturers is to find out if these diabetes medications are safe and effective for people with heart failure and no diabetes. If they are, a whole new market would open up for the SGLT2 and GLP-1 agents.

Bridging the gap from treating diabetes by lowering blood sugar to lowering blood sugar and simultaneously reducing the risk of cardiovascular disease with a single medicine is a huge leap forward for diabetes treatment with important implications for endocrinologists, primary physicians, and cardiologists. But the FDA’s approval occurred without a ringing endorsement from its advisory review panel, which barely recommended approval in a 13–12 vote. Review panel experts expressed concerns about the EMPA–REG OUTCOME study results and whether Jardiance was really the cause of the favorable cardiovascular outcome.

EMPA-REG OUTCOME was a postmarket, randomized, controlled trial with three primary endpoints—cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. It followed 7,020 patients with inadequately controlled type 2 diabetes and confirmed cardiovascular disease. All participants were treated with the diabetes and cardiovascular medications they were taking plus either Jardiance or a placebo. About 30% were taking one medication for diabetes and about 70% were using multiple medications. Approximately 80% of were taking renin–angiotensin system inhibitors; 65%, beta blockers; 43%, diuretics; 77%, statins; and 86%, antiplatelet agents (usually aspirin).

The study’s reduction in mortality was a concern because it occurred with no change in the risk of nonfatal myocardial infarction or nonfatal stroke. On top of that, the trial surprised everyone with an unexpected 35% reduction in hospitalizations for heart failure, which was not considered a primary outcome.

Curious results
“The results of the study were rather strange. They seem to be driven by heart failure admissions, not by heart attacks or strokes, and for that reason it has been difficult to understand exactly what the study means,” says Alan Garber, MD, past president of the American Academy of Clinical Endocrinologists. It’s hard to understand exactly what they mean.
of Clinical Endocrinologists (AACE). Moreover, says Garber, some of the enthusiasm has been tempered “by the fact there was no obvious mechanism of action to predict this outcome.”

Some caution
The AACE has moved cautiously in reacting to Jardiance’s new cardiovascular indication. The approval was noted in the 2017 update to its diabetes algorithm, but at the advisory committee meeting AACE president George Grunberger, MD, commented: “So should every patient with type 2 diabetes today be placed on empagliflozin or at least a SGLT2 inhibitor? We believe that would be premature because we have only one study and only one component of the primary endpoint, which was significantly positive.” It would have been better if EMPA–REG OUTCOME had shown a significant reduction in the risk of nonfatal myocardial infarction or nonfatal stroke to go along with the reduction in deaths.

It is a generalization, so there are certainly exceptions, but cardiologists seem to have reacted more positively to Jardiance’s cardiovascular indication. The approval is a “big deal,” says Mikhail Kosiborod, MD, a professor of medicine at the University of Missouri–Kansas City School of Medicine. “I suspect that this will have a substantial impact on how patients with type 2 diabetes and established CVD are managed and will, ultimately, improve the care and outcomes of this very high-risk-patient population.”

He emphasizes, though, that Jardiance was added to the diabetes and heart disease medications people were already taking and “therefore, I do not believe that the new indication for empagliflozin should have an impact on other treatments commonly used in patients with type 2 diabetes and CVD.”

Still, Kosiborod believes that Jardiance and medications like it could change and expand the role of cardiologists in diabetes care: “The strategy of treating patients with type 2 diabetes and established CVD may shift from the predominant focus on HbA1c control to the new paradigm where reduction in CV risk is prioritized along with HbA1c control.”

Boehringer Ingelheim sees an opening for Jardiance. It has two clinical trials to formally test Jardiance’s ability to reduce heart failure admissions, says Thomas Seck, MD, vice president of clinical development and medical affairs.

Meanwhile, results from CVD–REAL, a real-world study of 364,828 patients in six countries, were presented at the American College of Cardiology’s scientific meeting in March. They showed that SGLT2 inhibitors were associated with a 39% lower rate of hospitalizations for heart failure compared with other glucose-lowering medications, and, as a secondary outcome, a 51% decrease in deaths from all causes. Evan Sisson, an associate professor at Virginia Commonwealth University, says there is increasing interest in the apparent favorable effects the SGLT2 inhibitors have on heart failure, with anecdotal observations suggesting that they may reduce the need for diuretics in diabetes patients with heart failure.

Competition from GLP-1 agonists
Jardiance and its fellow SGLT2 inhibitors can’t rest on their laurels, because the GLP-1 agonists are also showing that they might have a positive effect on cardiovascular outcomes for people with diabetes. Results from the LEADER trial reported last year showed Victoza reduced death from cardiovascular causes by 22% and nonfatal myocardial infarction and stroke by 13%. Cardiovascular results reported last year for Novo Nordisk’s GLP-1 agonist, semaglutide, were also solidly in the plus column, and approval is now in the hands of the FDA.

One advantage the GLP-1 agonists have over the SGLT2 inhibitors may be greater weight loss. For the GLP-1 agonists, it’s in the range of seven to 10 pounds compared with two to five for the SGLT2 inhibitors. Of course, weight loss translates into reduced cardiovascular risk, so this isn’t just a matter of improving appearance.

Regardless of the outcome of the SGLT2 inhibitor and GLP-1 agonist competition, the larger picture here is that medications to treat diabetes seem on the verge of breaking out of their traditional lane. Instead of just controlling blood glucose levels, they are demonstrating a broader effect that could help people with diabetes avoid the dire cardiovascular outcomes associated with the disease.

If the results of a recent batch of clinical trials and real-world evidence studies hold up, patients will benefit—and so shall the revenues of the manufacturers of these medications with a diabetes–heart disease one-two punch. MC
In November 2010, David Mitchell was diagnosed with multiple myeloma. At the time, he thought the relatively rare bone marrow cancer—about 30,000 cases are diagnosed each year—would be the proverbial death sentence.

Things did not work out that way—thankfully. Last month, Mitchell celebrated his 67th birthday with a dream-come-true Grand Canyon rafting trip with his son.

And a big reason why the retired health care communications expert is still very much alive is Celgene's Revlimid, a thalidomide analogue, which the FDA approved and designated as an orphan drug for treatment of multiple myeloma in 2001.

Now Mitchell is on another orphan drug, Takeda Oncology's Velcade, which he takes in combination with Darzalex, a non-orphan drug marketed by Janssen. The retail price (as shown in his insurer's explanation of benefits) for the combination, which is infused over 4.5 hours, is $20,000 per treatment, Mitchell says. He expects to have 22 treatments over 12 months. Do the math. If his insurers—Medicare Part B and UnitedHealthcare—pay the amount in the explanation of benefits, they'll shell out $440,000 for his treatment.

Even nowadays, when six-figure drug prices fail to impress, Mitchell's treatment rates as expensive. But Mitchell is not complaining about his personal costs for the two orphan drugs he's taken—or about Darzalex, for that matter. He was fortunate to have good employer coverage and now, in retirement, he can afford a Medicare supplemental policy that limits his financial exposure. His out-of-pocket expenses for Revlimid were about $3,250 per year when the dose that he was taking was priced at more than $125,000 per year. Mitchell saw the price of Revlimid shoot up by 34% while he was on the drug and his out-of-pocket mushroomed by almost 600%.

Way Too Many, Way Too Expensive
Sales hit the billion-dollar mark as pharmaceutical companies have used the Orphan Drug Act to their advantage. Insurers are beginning to push back.

By Joseph Burns
Contributing Editor

Orphan approvals by year
The Orphan Drug Act of 1983 helps drug companies turn a profit, but gives insurers and other payers headaches. The past decade has been a bonanza for first-time orphan drugs, with approvals more than doubling. In 2015, there was a record 37 of them. Drug companies often receive secondary orphan approvals to treat other diseases, or just subcategories of the original diseases. The perennial question: How to pay for them?

Source: FDA's Orphan Drug Database
Still, Mitchell recognizes that it’s no small thing that he has had access to lifesaving drugs that weren’t available just a few years ago.

“I am very, very grateful for those drugs to treat multiple myeloma,” says Mitchell, a resident of Potomac, Md., and founder of a new group called Patients for Affordable Drugs that bills itself as the only patient organization free of pharmaceutical company influence that is pushing to lower drug prices. “I want drug companies to be compensated for developing orphan drugs even though these drugs generally are supposed to be used for very small populations. But high drug prices—they are hurting people.”

Like many others, Mitchell says drug companies are manipulating the law that created the orphan drug status. He mentions the “salami slicing” strategies—companies dividing diseases into smaller and smaller categories based on genetic and biomarker differences so their products can achieve the coveted orphan drug status.

“This gaming of the system to cut and recut for different orphan diseases means they get to use the same drug for multiple orphan drug designations,” says Mitchell. “That needs to stop.”

Busy orphanage
The Orphan Drug Act (ODA) was designed to remedy the economics of developing drugs for unusual diseases. Development costs are high and with a relatively small number of affected people, there is little chance of sales yielding a profit. So in exchange for developing a drug with a market of fewer than 200,000 Americans, a drug company gets as many as four years’ worth of subsidies totaling as much as $500,000 annually, tax credits, waived FDA application fees that can total $2 million, and seven years of rights to market the drug exclusively.

Painting with a broad brush, the law has worked. Since 1983 when President Reagan signed the law, more than 200 drug makers have introduced some 450 orphan drugs. EvaluatePharma’s 2017 report on orphan drugs predicts that annual worldwide sales will climb by 11% annually, to $209 billion, in the next five years and grow about twice as fast as prescription drug sales overall.

That’s great news if you are a drug developer or pharma company. But payers, providers, patients, and academics say the Orphan Drug Act is pouring gasoline on the fire of escalating drug costs.

Some commentators have said the trouble starts with the law’s prevalence-based definition of a rare disease as a condition that affects fewer than 200,000 individuals. Because drug companies can now price orphan drugs at between $100,000 to $200,000 per patient per year, they need only 5,000 to 10,000 patients to hit the blockbuster mark of $1 billion in annual sales.

But there’s also plenty of evidence and attendant criticism that the law’s intended purpose of encouraging the development of drugs for rare diseases has been undermined in various ways.

In January, Kaiser Health News published the results of a six-month investigation of the law and how it has been applied. “While the companies are not breaking the law,” the health news service concluded, “they are using the 1983 Orphan Drug Act to secure lucrative incentives and gain monopoly control of rare disease markets where drugs often command astronomical price tags.” The Kaiser news service—which is independent of the Kaiser Family Foundation and not affiliated with Kaiser Permanente health plan—found that drug companies had gotten orphan status for more than 70 drugs that the FDA had initially approved for mass market use, including Crestor, Abilify, and Humira.

After the Kaiser series ran, Sen. Chuck Grassley, an Iowa Republican, announced that he was considering how the law could be revised. In March, the Government Accountability Office said it would begin to investigate the orphan drug approval process, although that review won’t start until later this year.

Rescind exclusivity
One way to minimize the ability of drug makers to use the orphan drug rules to their advantage would be to make market exclusivity flexible, says Dyfrig A. Hughes, a professor of pharmacoeconomics and co-director of the Centre for Health Economics and Medicines at Bangor University in Wales. In an article
It’s not unusual for “orphan markets” to get quite large if the market is no longer small, Hughes asks. He argues benefiting from the orphan drug above 200,000 patients, original group of patients that push the number beyond orphan designation if a company adds individuals to its pool, showing that publicly traded pharmaceutical companies in the United States and Europe that had orphan drugs among their products had higher market values and greater profits than companies not producing treatments for rare diseases.

There’s no reason the FDA couldn’t withdraw an orphan designation if a company adds individuals to its original group of patients that push the number beyond orphan designation if a company adds individuals to its pool, showing that publicly traded pharmaceutical companies in the United States and Europe that had orphan drugs among their products had higher market values and greater profits than companies not producing treatments for rare diseases.

Hughes and other experts say slicing diseases into smaller and smaller categories means Congress, the FDA—or perhaps both—need to act soon to reform the Orphan Drug Act. Oncology is especially fertile territory. The 1983 law is no longer sustainable, Hughes argues, because the growing sophistication of genetic tests of tumor cells and the increasing specificity of some medications mean almost any cancer drug can be maneuvered into the orphan drug category.

Researchers in the United States make similar arguments. In an article published last year in the *American Journal of Clinical Oncology*, Michael Makary, MD, a professor at Johns Hopkins, and his colleagues discussed how Herceptin, originally approved as a breast cancer drug, has gained orphan designation for pancreatic and gastric cancers because those cancers can now also be classified as HER2-positive and HER2-negative.

**“The spirit of the Orphan Drug Act is not quite being followed because, in fact, drugs are being used in much larger markets,” says Steven Joffe, MD, of the University of Pennsylvania.**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>Generic name</th>
<th>Company</th>
<th>US sales (f)</th>
<th>Revenues per patient 2016</th>
<th>No. of patients 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Revlimid</td>
<td>lenalidomide</td>
<td>Celgene</td>
<td>4,417</td>
<td>113,887</td>
<td>38,301</td>
</tr>
<tr>
<td>2</td>
<td>Rituxan</td>
<td>rituximab</td>
<td>Genentech and Biogen</td>
<td>3,970</td>
<td>61,099</td>
<td>65,286</td>
</tr>
<tr>
<td>3</td>
<td>Copaxone</td>
<td>glatiramer acetate</td>
<td>Teva</td>
<td>3,257</td>
<td>56,427</td>
<td>57,728</td>
</tr>
<tr>
<td>4</td>
<td>Opdivo</td>
<td>nivolumab</td>
<td>Bristol-Myers Squibb</td>
<td>2,664</td>
<td>43,083</td>
<td>60,579</td>
</tr>
<tr>
<td>5</td>
<td>Avonex</td>
<td>interferon beta-1a</td>
<td>Biogen</td>
<td>1,675</td>
<td>71,752</td>
<td>23,425</td>
</tr>
<tr>
<td>6</td>
<td>Imbruvica</td>
<td>ibrutinib</td>
<td>AbbVie and Janssen</td>
<td>1,580</td>
<td>126,040</td>
<td>12,775</td>
</tr>
<tr>
<td>7</td>
<td>Sensipar</td>
<td>cinacalcet hydrochloride</td>
<td>Amgen</td>
<td>1,240</td>
<td>6,196</td>
<td>198,130</td>
</tr>
<tr>
<td>8</td>
<td>Gleevec</td>
<td>imatinib mesylate</td>
<td>Novartis</td>
<td>1,114</td>
<td>104,202</td>
<td>10,486</td>
</tr>
<tr>
<td>9</td>
<td>Velcade</td>
<td>bortezomib</td>
<td>Takeda</td>
<td>1,133</td>
<td>55,691</td>
<td>20,353</td>
</tr>
<tr>
<td>10</td>
<td>Xyrem</td>
<td>sodium oxybate</td>
<td>Jazz Pharmaceuticals</td>
<td>1,114</td>
<td>73,899</td>
<td>15,074</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma, February 2017

published last year in *PLoS ONE*, Hughes and Jannine Poletti-Hughes, a lecturer at the University of Liverpool, showed that publicly traded pharmaceutical companies in the United States and Europe that had orphan drugs among their products had higher market values and greater profits than companies not producing treatments for rare diseases.

Instead of an automatic seven years of market exclusivity, Hughes suggests the companies be required to make the business case for patent protection and leave it open for inspection every year. Regulators could decide that a product would be sufficiently profitable within three years or five years or so. On the other hand, if a company making an orphan drug failed to turn a profit after an initial few years, it could present new evidence in a request for additional years of patent protection.

There’s no reason the FDA couldn’t withdraw an orphan designation if a company adds individuals to its original group of patients that push the number benefiting from the orphan drug above 200,000 patients, he argues.

“Why shouldn’t the period of exclusivity be terminated if the market is no longer small?” Hughes asks. It’s not unusual for “orphan markets” to get quite large because drug companies add indications, some of which could be for common diseases, he says. In such cases, the FDA might rescind or modify orphan status.

This is not an unfamiliar idea. The House and Senate passed legislation that would have ended market exclusivity once a drug was used by more than 200,000 people in 1990 but President George H.W. Bush vetoed it.

Hughes and experts say slicing diseases into smaller and smaller categories means Congress, the FDA—or perhaps both—need to act soon to reform the Orphan Drug Act. Oncology is especially fertile territory. The 1983 law is no longer sustainable, Hughes argues, because the growing sophistication of genetic tests of tumor cells and the increasing specificity of some medications mean almost any cancer drug can be maneuvered into the orphan drug category.

Researchers in the United States make similar arguments. In an article published last year in the *American Journal of Clinical Oncology*, Michael Makary, MD, a professor at Johns Hopkins, and his colleagues discussed how Herceptin, originally approved as a breast cancer drug, has gained orphan designation for pancreatic and gastric cancers because those cancers can now also be classified as HER2-positive and HER2-negative.

**“Every medication can be an orphan”**

Makary and his coauthors note that one solution to this version of salami slicing would be to test and approve cancer drugs based on the molecular profile of the cancer, not the organ of origin. So, for example, drugs active against HER2-positive cancers would be approved for all HER2-positive cancers and not for HER2-positive breast cancer, HER2-positive gastric...
Walgreens provides the patient-focused specialty pharmacy access necessary to consistently deliver better outcomes. With over 250 specialty pharmacies, and access to specialty medication at every retail location, we’re improving adherence rates and changing how our partners think about specialty medicine.

To learn how Walgreens can make a difference for your members, please visit Walgreens.com/HealthSolutions

Staskon F, Fu C, Kirkham H. Multiple Sclerosis Medication Adherence within Walgreens Local Specialty Pharmacies is Significantly Higher Compared to Other Class of Trade Pharmacies. AMCP Managed Care & Specialty Pharmacy Annual Meeting. 27 Mar 2017.
cancer, and so on. “The current system of classifying by both organ of origin and molecular identity is creating a situation wherein almost every medication can be an orphan,” they wrote.

Pricing, profit, and the possibility of a blockbuster therapy are among the reasons the orphan drug market has become so attractive for the nation’s largest pharmaceutical companies, notes Enrique Seoane Vazquez, an associate professor and director of the International Center for Pharmaceutical Economics and Policy at the Massachusetts College of Pharmacy and Health Sciences. Seoane Vazquez is one of the authors of an article published earlier this year in the Orphanet Journal of Rare Diseases on how to reconcile economic incentives and meet patients’ needs. When the orphan drug legislation was passed, small pharmaceutical companies and universities were developing medications for rare diseases, Seoane Vazquez says. “Right now, all the largest pharmaceutical companies are involved in the research and development of orphan drugs.”

Along with the change from small companies to larger ones, orphan drugs have become a major cost concern for affected patients, in part because of the advent of so many high-deductible health plans.

For these and other reasons, the orphan drug market needs more scrutiny from regulators and those with the power of the purse in American health, meaning private and public payers, says Steven Joffe, MD, an associate professor at the University of Pennsylvania Perelman School of Medicine and coauthor of an article published earlier this year on the biomarker-defined subsets of diseases.

Joffe and colleagues found that 16% of the orphan drugs approved from 2009 to 2015 were for subsets of common diseases defined by biomarkers. Given that the Orphan Drug Act was supposed to incentivize the development of drugs for low-prevalence conditions, the spirit of the law is not quite being followed if orphan drugs are being used by large numbers of patients because the drugs have multiple indications or are being used off-label, says Joffe.

**Pushback from insurers**

Insurers are beginning to push back some—not a lot, but some—on paying for orphan drugs with big price tags. In May, Harvard Pilgrim Health Care signed a contract with Amgen for its PCSK9 inhibitor, an LDL cholesterol lowering drug called Repatha. Under this contract Amgen will pay HPHC and its members a full refund if a member requires hospitalization for a heart attack or stroke after taking Repatha for at least six months and achieving an appropriate level of compliance. Designated an orphan drug in 2013, Repatha has market-exclusivity until 2022.

Last year, Anthem said that it would not cover Exondys 51, the controversial drug for Duchenne muscular dystrophy priced at $300,000 per patient per year. Despite FDA approval, Anthem said Exondys 51 was investigational and not medically necessary. FiercePharma reported that UnitedHealthcare would cover the drug, while Aetna and Express Scripts would review the clinical data before deciding on coverage.

Payers also are pushing back on Spinraza, the new

**Increasing value of orphan drugs**

Average expected lifetime revenue from orphan drugs vs. non-orphan drugs, adjusted for inflation, 2000 vs. 2010

US $millions

![Graph showing increasing value of orphan drugs](source: Meekings et al., Drug Discovery Today, July 17, 2012)
orphan drug for spinal muscular atrophy. After Biogen and Ionis set the price at $625,000 to $750,000 in the first year and $375,000 after that, Anthem said it would restrict coverage to those patients with the most severe form of the disease. Anthem and Humana said they would cover the medication after the first six months only if Biogen and Ionis could prove that patients were responding to treatment positively. UnitedHealthcare said it would cover the drug for patients with spinal muscular atrophy but added seven conditions that patients must meet.

Such scrutiny will be necessary because it's possible to classify so many diseases as rare, Joffe says.

“I don’t think we’ll get to the point where every person has a unique disease, but we are going to move toward the point where rare diseases are the norm,” he comments. In fact, that’s the goal of precision medicine. “We want everybody to be part of some small subset that we can target for some rational targeted therapy,” he says.

**Payment models**

So if rare diseases are the new normal, then, asks Joffe, how do health insurers make appropriate coverage decisions? While there are no easy answers to this question, health insurers are tinkering with new forms of payment that could be applied to orphan drugs.

Mark Trusheim, an economist and visiting scientist at the MIT Sloan School of Management, is working with health insurers, regulators, pharmaceutical companies, academics, and patient advocacy groups to develop new financing models particularly for medications, including orphan drugs. Among the ideas under consideration would be a definition of metrics to assess the value of medications for patients whose clinical biomarkers are used to identify therapeutic agents and new pricing models based on these metrics, he said.

Trusheim’s group has been working for about a year and hopes to release its recommendations next year. “But we’re not ready to state what any of those are yet,” he says.

In the meantime, experiments with different payment models and value-based care might tap the brakes on orphan drug costs. For two years, Anthem has paid physicians $350 per patient per month under its Cancer Care Quality Program, according to a recent article in the *Milbank Quarterly*. The $350 supplements fee-for-service payment for office visits and cost-plus payment for office-administered drugs, and is designed to get doctors to follow Anthem’s recommendations for drug treatment regimens, except when specific patients need off-pathway treatment, wrote James Robinson, the author of the *Milbank Quarterly* article.

The monthly payment for each Anthem patient in chemotherapy serves as an incentive for physicians to submit clinical data and adopt Anthem-approved drug pathways. In return, Anthem asks physicians to enter clinical data not usually available from claims, including biomarker test results, tumor type, and disease stage. Anthem intends to use the data to develop risk-adjusted quality metrics for payment.

The program is not being used for patients with orphan diseases specifically, because there’s usually just one medication per orphan-drug indication, Robinson said in an email to *Managed Care*.

What would carry over, however, is some form of hybrid payment method that combines fee-for-service payment for office visits with a monthly or every-six-months payment per patient as a care management fee, explained Robinson, a health economist at the University of California–Berkeley. “The fee could be ‘financed’ by limiting the buy-and-bill markup on infused orphan drugs,” he noted. Some orphan drugs are not infused, however, meaning physicians get no markup and so the strategy would not work for those medications.

There is also the “soft power” of developing ongoing relationships with providers, usually specialists, who prescribe orphan drugs. “The drug companies have already developed close relationships with these specialists since each one is a major revenue source,” Robinson noted. Specialists don’t usually welcome insurers and pharmacy benefit managers with open arms, but they may be more receptive because of the number and high prices of orphan drugs and because of the offer of an additional monthly fee.

Robinson would get no argument from Mitchell, a believer in value pricing. “All drugs, including orphan drugs, should be put through a value framework analysis,” he suggests. That analysis would include whether the drug is better than existing medications and would adjust for toxicities and development costs. Rather than setting a price at whatever the market can bear, the manufacturer could adopt the recommended value-based price and insurers could waive copayments. “That way,” says Mitchell, “patients and insurers are rewarded with a reasonable price, and some of the savings go toward payment relief.”
Orphan Drug Debate: A Cheat Sheet

By Krishna R. Patel, PharmD  In some respects, the 1983 Orphan Drug Act is a success story. It changed the economics of developing drugs for rare diseases, so hundreds of treatments for diseases that affect relatively small numbers of people are now on the market. But high prices and allegations that some drug companies have twisted the law to their advantage have made it controversial. Here are some of the main points in the debate.

<table>
<thead>
<tr>
<th>What payers say</th>
<th>What manufacturers say in defense</th>
<th>What patients, providers, and experts are saying</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALMOST UNLIMITED PRICE TAGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturers charge premium prices for orphan drugs and payers have almost no choice but to pay for them.</td>
<td>Research and development for orphan drugs is long, costly, and risky.</td>
<td>Even though many patients and their families don’t pay the full amount for orphan drugs, high prices make access doubtful.</td>
</tr>
<tr>
<td>Median cost per patient in 2016 was 5.5x higher for orphan drugs compared with non-orphan drugs ($83,883 vs. $15,239, respectively).</td>
<td>High prices are a reflection of the high cost of developing new orphan drugs. Some companies focus on a therapeutic area for 20 or 30 years and never turn a profit. For example, it took 25 years for the development of an effective therapy for cystic fibrosis.</td>
<td>Insurance coverage and manufacturers’ patient-assistance programs help to lower the out-of-pocket costs for patients.</td>
</tr>
<tr>
<td>Payers are forced to cover orphan drugs because they are the only options available for patients.</td>
<td>Budget impact of orphan drugs is actually small. • ~1% of total U.S. health care spending. Payers are overstating the impact of high orphan drug prices; they cite high orphan drug prices as the reason for climbing premiums, copays, and coinsurance. However, rising medical costs have a much greater impact on rising costs.</td>
<td>• Patient-assistance programs are unavailable to patients covered by Medicare and Medicaid.</td>
</tr>
<tr>
<td>Uncertain long-term benefit. Orphan status has become synonymous with astronomical prices. It’s hard for payers to rationalize spending so much money in the first year of treatment without knowing the long-term effectiveness of the orphan drugs.</td>
<td></td>
<td>• Critics say manufacturers use patient-assistance programs to boost sales, burdening payers with the cost of covering high-priced drugs.</td>
</tr>
</tbody>
</table>

**RAPID GROWTH IN ORPHAN DRUG SALES**

<table>
<thead>
<tr>
<th>Payers feel it is unsustainable to shoulder the rapid growth in orphan drug sales in the past four to five years. Currently, only 5% of rare diseases have treatment options; what happens if that was 95%?</th>
<th>Rising concerns about the explosion of spending on orphan drugs are overblown.</th>
<th>The Orphan Drug Act has saved lives and relieved suffering for many Americans with rare diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide annual sales from orphan drugs are projected to grow twice as fast as the rate predicted for conventional drugs through 2020, according to market watcher EvaluatePharma.</td>
<td>Reason for rapid growth in costs is due to an increase in FDA approvals in recent years—and that is a good thing. The number of orphan drug approvals increased from 16 in 2007 to 33 in 2013. U.S. orphan drug expenditures will actually remain fairly stable in proportion to total pharmaceutical expenditure (8.8% in 2014 to 9.5% in 2018), according to a study published in Health Affairs.</td>
<td>Despite the increasing number of orphan drug approvals in recent years, an unmet need exists even today, as only 5% of rare diseases have a treatment.</td>
</tr>
<tr>
<td>Worldwide sales of orphan drugs are expected to almost double between 2016 and 2022 to $209 billion, accounting for 21.4% of total worldwide prescriptions sales, according to EvaluatePharma.</td>
<td>True impact of orphan drugs has been overstated in many studies that lump orphan drugs in with specialty medicines and precision medicines.</td>
<td>Development of orphan drugs has added extraordinary value for patients. Patient advocacy organizations and disease charities are the ones that push for initiation of research for orphan drugs. Note: Some say the advocacy groups and disease charities are too cozy with industry and are being used.</td>
</tr>
<tr>
<td>Expenditures for oncology were the highest among all major therapeutic areas. The next major therapeutic areas were infections, nononcology hematology, and metabolic disorders.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Krishna R. Patel is a senior medical writer at MediMedia Managed Markets, a division of ICON plc.
A loophole in the Orphan Drug Act allows manufacturers to receive market exclusivity for older drugs that are already available in markets outside the U.S.

**Partial orphan drugs** (drugs initially approved for the mass market that subsequently gain an indication for a rare disease) are rampant.

- Examples include Crestor, Abilify, Herceptin, Botox, and Humira.

**Salami slicing** (artificially slicing the disease into smaller subgroups in order to gain orphan status and reap the accompanying benefits such as premium price tags, 50% tax credit on R&D costs, and seven years of market exclusivity) is another way manufacturers are taking unfair advantage of the law.

- Drugs indicated to treat **biomarker-defined subsets of common conditions**, especially cancer, comprised 16% of recently approved orphan drugs.

**Priority review vouchers have been sold** and been known to fetch up to $350 million by manufacturers of orphan drugs in the open market.

**Sources:**
When Biogen won regulatory approval late last year for a new drug to treat a spinal muscular atrophy, a rare genetic disorder in children, the price tag quickly sparked debate. The first year of treatment costs an eye-popping $750,000 and each year thereafter runs a hefty $375,000.

Given the growing anger and anxiety about the cost of medications in this country, one Wall Street analyst worried the price tag for Spinraza might become “the straw that breaks the camel’s back in terms of the U.S. market’s tolerance for rare disease drug pricing.”

So far, though, Spinraza is rolling right along. Biogen recently reported $47 million in sales in the first quarter, three times Wall Street expectations. And there are “numerous reasons” why sales should continue climbing, Cowen analyst Eric Schmidt wrote in an investor note.

The performance reflects the ongoing allure of orphan drugs for the pharma and biotech companies. Under the 1983 law that created separate approval rules for treatments for rare diseases, orphan drugs are defined as medications that target patient populations of 200,000 or less. Sales of orphan drugs are forecast to grow 11% over the next five years, to $209 billion. That growth rate is twice as fast as the expected increase in sales of all other prescription medicines, according to EvaluatePharma. By 2022, EvaluatePharma predicts that orphan drugs will account for more than 21% of worldwide brand-name prescription drug sales, up from 6% in 2000.

These figures suggest that orphan drugs will remain a lucrative revenue stream for drug makers for years to come. Insurers may think about putting up hurdles to coverage, but haven’t for a couple of reasons. Sometimes the number of patients is so small that the added expense isn’t worth fighting over, and no insurer wants to be put in the position of denying coverage of serious, life-threatening conditions.

“On the pricing front, for those drugs that are new chemical entities or first approaches to these diseases, we don’t see any pricing pressure,” says SunTrust Robinson Humphrey Analyst Edward Nash.

Recent history certainly supports this outlook. Last year, there were 582 requests for an orphan designation from the FDA, a 23% increase from 2015 and triple the number of requests that were made a decade ago. The number of designations last year totaled 333, down slightly from 354 in 2015, but still the second-largest number ever. And the FDA approved 39 orphan drugs last year, which is fewer than the number approved in the two previous years but the third-largest tally.

Some pushback may be coming. Fifty-three percent of 34 biotech executives and large investors believe payers will be tougher over the next year or two, according to a SunTrust Robinson Humphrey survey.

One payer confirms this perspective. “We are consistently monitoring pipelines and looking for new drugs and new indications that would contribute to new spending,” says April Kunze, senior director for clinical program development at Prime Therapeutics, a pharmacy benefits manager in Minnesota. “It’s been challenging over the past six to nine months.”

Last year, Prime’s overall spending on medicines totaled $22.6 billion and specialty drug spending accounted for 30%, or roughly $6.8 billion, a Prime spokesperson says. Orphan drug spending was between 10% to 20% of the specialty drug spending, or $600 million to $700 million. As a result, Prime looks religiously at codes to match indications, the number of people in the population that may have the diagnosis, and recent clinical trial results “to get some idea of utilization and cost trends,” Kunze explains.

Even so, the SunTrust Robinson Humphrey survey found that investors, more than biotech executives, expect near-term pricing pressure and, interestingly, 31% of the executives, compared with 9.5% of investors, do not believe orphan drug pricing will become a serious issue in the next decade.

“I think companies are trying to be as conservative as possible, at least with regard to how they speak to the Street,” says Nash. “No doubt, these [drugs] will be expensive. But to start putting pressure on pricing would almost go against the whole spirit of the orphan drug incentive.”

Ed Silverman founded the Pharmalot blog and has covered the pharmaceutical industry for 20 years.
Readers Want Reforms of Orphan Drug Act

Like many other others, they see orphan drugs as being something of a problem child in American health care these days. But *managed care* readers largely agree on several reform notions designed to lower prices and limit market exclusivity.

More than half (53%) of the 111 respondents to an online survey rated orphan drugs as having a major impact on rising drug costs, although there was also fairly wide (if mild) agreement that the 1983 Orphan Drug Act has been successful in creating incentives to develop remedies for rare diseases.

The assertion that the pharmaceutical industry is gaming the orphan drug approval process was met with approval: 64% of the respondents strongly agreed with that statement. And, not surprisingly, a similar proportion agreed with ideas to change the Orphan Drug Act that are supposed to curb the alleged gaming, including restrictions or elimination of “salami slicing” diseases into subsets to get orphan drug status and taking away orphan drug status if sales for a drug reached a certain threshold—for example, the $1 billion blockbuster mark.

Medimedia Research conducted this online survey of *managed care* readers from May 2 to May 11. MediMedia Research is a part of MediMedia Managed Markets, an ICON plc company, and the owner of *managed care*.

Source for all charts: MediMedia Research
In January, a new venture investment fund opened in Boston with $42 million in its pocket and a goal of raising $80 million within two years. The new fund, called the JDRF T1D Fund, quickly invested in three early-stage start-ups. Just like traditional venture capital funds, the T1D Fund plans to work closely with start-ups in its specialized niche. Its corner of the world is type 1 diabetes, or T1D for short, thus the fund’s name.

The difference between the T1D Fund and conventional venture funds is its source of funding and what it does with any returns on investment. The typical venture capital fund wants profits that can be turned into a major return for investors in a relatively short period of time—say, five years or so. The T1D Fund is an example of a relatively new form of funding known as venture philanthropy. Instead of investors, there are donors, and the money they put up is considered a donation for income tax purposes. Instead of profits going to investors, revenues in excess of expenses are supposed to be plowed back into new investments supporting the mission. The T1D Fund has been capitalized by the New York City-based JDRF (formerly the Juvenile Diabetes Research Foundation) and individual donors.

Jonathan Behr, managing director of the T1D Fund, says it is the first investment vehicle of scale devoted to early-stage commercial investing in treatments for type 1 diabetes. “We think it has the opportunity to accelerate outcomes. It’s true venture philanthropy in that all the capital coming into the fund is a donation,”
says Behr, who was an executive at Partners Healthcare Innovation in Boston before the T1D Fund.

The T1D Fund seeks to “de-risk” promising opportunities in type 1 diabetes research so they will eventually attract investment from more conventional investors like venture capital funds and drug companies, explains Behr. JDRF, as a major donor, provides Behr and others at the T1D Fund with scientific, drug development, regulatory, and reimbursement expertise. The first investment was in Bigfoot Biomedical, which has developed an automated insulin delivery system that has been compared to an artificial pancreas.

**Some new treatments**

Philanthropies to support noble causes has its roots in the early 20th Century, when steel tycoon Andrew Carnegie created the Carnegie Foundation to “promote the advancement and diffusion of knowledge and understanding.” Traditional big-dollar secular philanthropy was a matter of well-endowed foundations giving to not-for-profit institutions.

But venture philanthropy and the move toward investment of not-for-profit dollars in for-profit companies started about 10 years ago. Initially, the focus was on education and housing, but now disease-related efforts are becoming popular. Venture philanthropy as a way to fund the development of drugs for rare diseases independent of governments and industry has already led to some new treatments.

But venture philanthropy is not without its problems and critics. Some see it as warping the purpose of charities and patient organizations, so they wind up serving the interest of private drug development. Elizabeth Rosenthal, editor in chief of Kaiser Health News, is critical in her new book, *An American Sickness*. With venture philanthropy, a new breed of executive took over medical foundations, she writes: “Fundraising rather than curing disease often seemed like the first metric of success.” And so far, venture philanthropy has done nothing to stop—and, in fact, may help fuel—the upward spiral of drug costs.

Alexandra Graddy-Reed, a researcher at the Center on Philanthropy & Public Policy at the University of Southern California, says venture philanthropy isn’t the same as venture capital investment, but there’s overlap. It does aim to make grants more like an investment. Funders have a more involved relationship with the grantees, and milestones need to be met. “Evaluation and measurement are key,” she says.

Venture philanthropy is especially productive for charities that focus on rare diseases that, until fairly recently, didn’t get much attention from pharmaceutical and biotechnology companies and were not a priority of government funders. “Venture philanthropy is a good strategy if you can incentivize companies to do the research that has a lot of potential,” Graddy-Reed says.

JDRF is not a newcomer to venture philanthropy and has invested in several industry partnerships over the past decade. For example, in 2012, it teamed up with KalVista Pharmaceuticals, in Cambridge, Mass., to develop plasma kallikrein inhibitors to treat diabetic macular edema. KalVista subsequently raised $33 million in 2015 in Series B equity financing for its research and clinical development programs on plasma kallikrein inhibitors. “The phase 1 U.S. clinical study, which we co-funded with the company, produced positive results and key proof-of-concept data,” says Michael Batten, director of research business development at the JDRF, which invested $2.2 million in KalVista. The data generated by the co-funded study allowed the company to raise its next round of funding.

JDRF has negotiated paybacks from its for-profit partners, typically in the form of commercial royalties upon approval of a therapy, which the foundation uses to further support its mission to cure, prevent, and treat type 1 diabetes. The T1D Fund will negotiate terms of its investments on a case-by-case basis and may make equity, royalty, and other types of investments, Behr says.

**Faster, please**

JDRF is part of a growing movement among diseasespecific charities frustrated by the seemingly glacial pace of academic research. Kristin Schneeman, director of programs at FasterCures, a not-for-profit think
tank that is part of the Milken Institute, says her organization runs training programs to encourage charity officials to think about new ways of funding outside organizations. The term “venture philanthropy” is limiting, she says, because many disease-research organizations are taking other kinds of outcomes-oriented approaches that might not involve investing in companies. According to Schneeman, it’s rare for charities to make equity investments. Royalty-bearing grants are more common, with payments made as milestones are met.

“Everybody gets into this business wanting to help patients ultimately, but the various and different incentive systems at play get in the way,” says Schneeman. “Patient groups are bringing the patients’ bottom line into the equation. There is a drive to create new and better treatments as quickly as possible.”

About a decade ago, the Cystic Fibrosis Foundation and a handful of other organizations started to rethink their roles and their funding models. The efforts by disease foundations that fit under the venture philanthropy umbrella include the Leukemia and Lymphoma Society Therapy Accelerator Program, the Dementia Discovery Fund, CureDuchenne, DELSIA (Delivering Scientific Innovation for Autism), the Cure Alzheimer’s Foundation, the National Multiple Sclerosis Society, the Multiple Myeloma Research Foundation, and the Michael J. Fox Foundation.

The Cystic Fibrosis Foundation has been a leading example of venture philanthropy—the success story that others want to emulate. The charity made a $3.3 billion windfall in 2014 from anticipated future royalties for the drugs Kalydeco, Orkambi, and other potential therapies of cystic fibrosis developed by Vertex Pharmaceuticals with foundation support. In 2012, the FDA approved Kalydeco, the first disease-modifying drug for cystic fibrosis, a heritable disease that affects about 30,000 Americans. The jaw-dropping price tag on the treatments: $330,000 per patient per year for Kalydeco and $266,000 per patient per year for Orkambi.

“[Kalydeco] is the most well-known of our investments,” says Preston W. Campbell III, CEO of the Cystic Fibrosis Foundation. “But it is far from our only success. Nearly every CF drug available today was made possible because of the foundation’s investments in drug discovery and development.”

Campbell says current projects include one with Genzyme focused on next-generation modulators and another with Editas Medicine, a Cambridge, Mass., company to explore gene editing. Cystic Fibrosis Foundation Therapeutics Inc. (CFFT), the CF Foundation’s nonprofit drug discovery and development affiliate, announced a $14 million expansion of its research agreement with Genzyme two years ago. Editas and the foundation announced a three-year agreement last year in which CFFT will pay up to $5 million to Editas to support the discovery and development of CRISPR/Cas9-based medicines for the treatment of cystic fibrosis.

The Cystic Fibrosis Foundation pioneered venture philanthropy because the pharmaceutical industry didn’t have enough financial incentives to invest billions of dollars and years of research to develop drugs for diseases such as cystic fibrosis that affect only a relatively small number of people. “The foundation’s venture philanthropy model was born out of this need,” Campbell says. “By providing upfront funding and reducing financial risk for pharmaceutical companies, the CF Foundation has made sure that this rare disease has not been ignored.”

Amazing Grace

The creation of the Grace Science Foundation offers a different angle on emerging, wide-ranging approaches to venture philanthropy. It’s the story of how a Silicon Valley executive is using his skills to support research on a disease that affects his daughter.

Grace Wilsey was born seven years ago with a rare genetic disorder, NGLY1 deficiency. Her body produces an insufficient amount of N-glycanase, an enzyme encoded by the NGLY1 gene.

The neurological syndrome is marked by abnormal tear production, a movement disorder (choreoathetosis), and liver disease. Additional features may

It's rare for charities to make equity investments; royalty-bearing grants are more common, says Kristin Schneeman, director of programs at the think tank FasterCures.
include developmental delay, hypotonia (weak muscle tone), peripheral neuropathy, EEG abnormalities, and a small head size (microcephaly).

“It’s a terrible disease,” says Matt Wilsey, Grace’s father. “What I tell people often is that the lights are on in the house, but no one is answering the door. She has little moments where I say to myself, ‘Oh, wow, she totally understands something.’ And then the rest of the day I think, ‘I’m not sure she understands anything I’m saying.’ She can’t communicate, which is the worst part about the disease.”

Initially, the Wilseys and their friends started supporting research at a handful of academic institutions to understand the disease and look for potential cures. But Wilsey, who has been involved in three startups, one of which was acquired by Twitter, saw that a lot more needed to be done. He and his wife, Kristen, started the Grace Science Foundation, based on the start-up model used in Silicon Valley. “It’s lean. It’s efficient. It’s very, very flat. There’s no hierarchy. We want to iterate very quickly. We don’t look at failure as a bad thing,” says Wilsey. The foundation has raised $6 million and recruited more than 100 scientists from around the world. Wilsey says patients’ families are heavily involved so researchers know firsthand what patients are experiencing.

The Grace Science Foundation expects researchers to share information with labs that otherwise might be their rivals to accelerate drug development. Molecular biologist Lars Steinmetz, co-director of the Stanford Genome Technology Center and group leader and senior scientist at the European Molecular Biology Laboratory, has worked with the foundation for four years. He believes that rare diseases such as NGLY1 deficiency call for “new paradigms in how science is done and drugs are developed. Large pharmaceutical companies are unlikely to invest in diseases like NGLY1 deficiency because there are only very few patients.” Steinmetz says the requirement to collaborate among multiple labs enables research to proceed much faster than it would with independent groups that do not communicate. Yet eventually, he says, a commercial partner will be needed: “When you come into it from an academic perspective, you have tools that you can launch against the problem, but you cannot replace an industrial setting to bring a drug to market and to do all the controlled experiments and the clinical trials that would be necessary.” Wilsey plans to launch a drug company separate from the foundation to develop medications for NGLY1 deficiency and related diseases.

Yet, the concept and practice of venture philanthropy raises some questions. Eric Campbell, director of research at the Mongan Institute Health Policy Center at Massachusetts General Hospital in Boston, sees venture philanthropy as a contradiction in terms. “The notion of venture philanthropy in some ways is oxymoronic. It’s like being an amateur–pro athlete.

Parental advocacy started the Grace Science Foundation. Matt Wilsey and his wife, Kristen, want to find the best treatment and, eventually, a cure for the rare genetic disorder NGLY1 deficiency that afflicts their daughter, Grace.
You’re either in a venture-related business and the goal of that is to make money or you’re in a philanthropy. But putting those two together doesn’t make much sense,” he says.

Venture philanthropy will likely change the motivations of not-for-profits because they are financially interested in the outcome. “In my opinion, they should be treated no different than a drug company,” he said. Moreover, just like any small pharma biotech company, they are facing long odds, says Campbell: “These organizations need to think very hard about their likelihood of a success, which to be honest is small. Drug companies that develop drugs for a living experience lots of failures in developing drugs. They rarely hit home runs.”

**Conflict of interest**

Paul Quinton, a researcher at the University of California–San Diego, has a unique perspective as a scientist specializing in cystic fibrosis because he is also a patient. Quinton, formerly a scientific advisor to the CF Foundation, said he was extremely grateful for the work the foundation has done to improve the health and extend the lifespan of patients. At age 72, "I’m twice as old as I’m supposed to be,” he jokes.

But he is troubled by the price tag for Orkambi and Kalydeco. “That’s a lot of people without any disease paying insurance to cover my drug cost. I feel a little guilty about that to tell you the truth. I don’t think I’m worth $300,000 a year to society,” Quinton says.

“So why should everybody else be burdened with making sure that the CEOs, the CFOs, and executive officers are making tens of millions of dollars a year in personal compensation from the cost of our drugs?”

The high cost for such drugs is unsustainable in his view. “Where will we get the money? And an even better question is, where is all that money going to go?”

Moreover, the foundation’s investments create a potential conflict for a charity. “It was like a doctor owning a drug company that makes drugs he then prescribes to his patients. He can’t do that. That’s a conflict of interest. So the CF Foundation was somewhat in the same situation in owning part of a company that provides drugs to their patients,” says Quinton, adding that charities that get involved in drug development are redefining altruism. “Is altruism for sale? Did the Cystic Fibrosis Foundation sell altruism because the money that they had to invest in Vertex/Aurora came from people who were altruistic?” he commented.

“The parents and the friends and the members of the CF community raised money and gave their time and money to the foundation. Is it still altruistic to pursue venture capitalism that profits a few with such extravagant costs to others? It is a rough question.”

---

**Desperately needed**

One question some advocates are asking about venture philanthropy is whether the not-for-profits involved could play a role in setting prices on drugs. Liz Piotrows, head of research and impact at the Association of Medical Research Charities (AMRC) in London, which represents 138 large and small British health charities, is skeptical about charities being able to lobby successfully for lower prices even on medications they helped develop. “We know that as patient organizations we can be a bit more emotional about affordability, as we are all too aware how much our patients desperately need new treatments. But we also know emotional arguments to industry won’t work,” she says.

Sharon Terry is the mother of two children with pseudoxanthoma elasticum (PXE), a progressive disorder characterized by the mineralization of tissue and co-founder of PXE International, a research advocacy organization. Terry, who has a theology degree, and her husband, Pat, a former construction manager, borrowed lab space at Harvard University and, tutored by postdocs, discovered the gene that causes PXE. They subsequently developed a diagnostic test, created a research consortium, and have started clinical trials.

Terry is also president of the Genetic Alliance, a network of disease organizations critical of the profits that pharma is making off of orphan diseases and the advocacy groups getting into venture philanthropy. “Most drug companies today, even the very large pharmaceutical companies, have opened rare disease divisions. It’s the thing to do now. And the reason they’re doing it is because their business model for blockbuster drugs has failed,” she says. “They are looking at the rare disease market with big eyes because they see that these drugs can garner hundreds of thousands of dollars a year per patient.”

Disease organizations and patient groups ought to have a hand in setting the price as part of their advocacy mission, says Terry, and her group pushes companies to set prices so they are affordable. “We’re not going to work with a company that’s going to go for a killing,” she says.

Conflicts of interest have to be carefully managed, says Schneeman at FasterCures, but she sees a role for not-for-profits getting involved in research and helping to get new products to patients. If the idea is good enough, one hopes that a company would carry the ball the rest of the way, she says. “I think a lot of patient groups are right now wrestling with whether they help support the development of drugs or not, or just purely play an advocacy role.”

Howard Wolinsky is an independent health care journalist based in Chicago.
When new pharmaceutical products enter the market, the lack of real-world experience with these drugs creates quandaries for payers and providers alike. Often, all there is to go on is the minimum required for FDA approval—non-inferiority to a comparator product in terms of efficacy and safety.

If an existing medicine is less expensive than the standard of care, payers typically have no ability to determine if the economic benefits of the new medicine will outweigh the cost of adding it to prescription coverage benefits. Uncertainty is one reason for the coverage caveat that patients first “fail” on a predecessor drug, which can also undermine the value proposition of the drug as demonstrated during clinical trials.

Hospitals are left with no real guideposts on whether to add new medicines to their formulary, let alone make recommendations for their use. Meanwhile, the medical staff is likely being pursued by pharmaceutical reps pointing to statistically random effects in subgroup analyses of trial data as support for expanded, off-label usage of the newly approved product.

Both payers and providers are in a position to use their market power to remove a good deal of this ambiguity. Here are a few promising strategies we suggest toward this end:

1. **Require evidence that medicines meet a threshold of cost-effectiveness.** Submission of an economic analysis by an objective third party should become a condition of health plan coverage and be used as a starting point for price negotiations with drug companies. Payers currently base reimbursement on the average wholesale price (plus a few percentage points), so drug makers are incentivized to inflate that figure as much as possible—well above what actual research and development costs warrant.

2. **Embrace clinical practice guidelines.** Hospitals and health systems, in particular, need to champion evidence-based, consensus-driven treatment guidelines, such as those published by the National Comprehensive Cancer Network.

   Moreover, the more they unite with payers on limiting access to expensive drugs for off-label purposes, the more likely physicians will do “everything possible” for their patients using evidence-based clinical trial data rather than their individual clinical judgment. Off-label prescribing is now too common. It should be reserved primarily for rare diseases and cancers for which all other options have been exhausted. Many drugs are used more broadly than intended—often without the patient’s knowledge—and it is a risky, sometimes harmful, business. Think Vioxx and fen-phen.

   Meanwhile, only about 4% of cancer patients are enrolled in clinical trials, and a scant 7% of trials are hitting their accrual targets. Coercing physician interest in research in this way would help reverse those trends and add statistical validity to the results—and get truly valuable drugs proven as such and more quickly brought to market for defined purposes and added to national consensus guidelines.

   Currently, drugs are often brought to market by studying the easiest population to accrue, such as the evaluation of antibiotics in patients with skin and soft tissue (SST) infections. In reality, there's a greater need of treatments for *Staphylococcus aureus* septicemia and pneumonia, but they are often not studied—or studied only after approval for SST—because doing so is more expensive and difficult.

3. **Avoid unnecessary and counterproductive step-therapy requirements.** Step-therapy requirements can get in the way of using a drug that is appropriate and cost-effective. For example, the lipoglycopeptides used to treat MRSA infections were tested as a one-time injection administered in the emergency department after which patients were sent home. The value proposition of the new treatment for MRSA infections lies in the avoidable admission, which should more than offset its higher upfront price. Yet many health plans are requiring that patients first fail a 10-day course of a conventional...
intravenous antibiotic that requires hospitalization and a great deal of follow-up.

4. Look for opportunities to enter into risk-based contracts with pharmaceutical companies. Drug companies are entering into a growing number of risk-or value-based contracts that require them to pay rebates if patients don’t benefit from a medication as advertised. For example, under some of the contracts for PCSK9 inhibitors, payers get reimbursed by the manufacturer if patients’ LDL cholesterol levels aren’t lowered to levels seen in clinical trials.

Some of these new contracts also require the manufacturers to pay rebates if prescriptions exceed a certain number. The goal is to encourage the use of lower-cost statins when appropriate.

An even better approach would be to tie the financial risk and rewards to preventing heart attacks.

Risk-based contracts should encourage negotiating partners of all kinds to invest in data analytics capable of teasing out connections between drug intake and patient outcomes. Some payers are already sharing risk with preferred oncology groups based on their adherence to clinical practice guidelines and actual patient outcomes.

5. Employ clinical–decision-support technology. Add-ons to electronic health record systems used by hospitals can constrain the utilization of high-cost drugs by limiting physicians to prescribing medicines for appropriate (FDA-approved) indications only. Tweaks to EHR software can also force substitutions.

But physicians generally respond best to suggested alternatives coupled with cost data. In our experience, they will almost invariably choose the least costly drug that meets the patient’s needs (and will find clever workarounds for any perceived red tape).

If a hospital elects to use decision-support technology in lieu of presenting physicians with data, a pharmacy stewardship committee will need to handle all of the special requests from physicians to veer from the utilization constraints and forced substitutions in the EHR. Community hospitals may find their pharmacy understaffed and lacking the skill to monitor misuse and uphold denials.

6. Assist in the development of value frameworks. The American Society of Clinical Oncology, Memorial Sloan Kettering Cancer Center, the American College of Cardiology, and other organizations are coming up with ways to determine if certain drugs are worth the investment from a pharmacoeconomic standpoint, and payers might want to add their voice to the dialogue. Some of these “value frameworks” are based partially on quality-adjusted life years with the suggested acceptable cost threshold ranging anywhere between $50,000 and $200,000. For a long time, $50,000 has been the accepted amount, although there is really no scientific basis for it.

The value assessment framework of the Institute for Clinical and Economic Review includes comparative clinical effectiveness, incremental cost per clinical outcomes achieved, and mechanisms to maximize health system value. Individual health systems, including Banner Health in Phoenix, are also grappling independently with how to define value in terms of both outcomes important to providers (e.g., readmissions, length of hospital stays, complication rates and death) and patients (e.g., complication rates and death but also nausea and vomiting, time spent in bed and at the doctor’s office, and how frequently a drug needs to be taken). The value frameworks physicians ultimately embrace will be the ones payers will want—or be forced by market pressures to use—as the basis for their prescription drug coverage policies. But physicians and payers will probably see eye-to-eye on value frameworks only after the knowledge gap between cost and outcomes has been bridged.

7. Centralize decision making of pharmacy and therapeutics (P&T) committees. P&T committees at the health system level could serve as reviewers-in-chief of postmarket surveillance data, which identifies adverse events seen only when a general population is exposed to a new drug.

The committees should also work to ensure that drug formularies across care sites and utilization of medicines are made consistent with established clinical guidelines. This is happening organically at growing numbers of health systems that are opening up their employee insurance plans to outside groups or, in other cases, partnering with established players and setting up retail pharmacies to further control costs.

Michael Schlosser, MD, is chief medical officer of HealthTrust, a group purchasing organization in Nashville. Ronald Chamberlain, MD, is a surgical oncologist and chief of surgery at Banner MD Anderson Cancer Center in Gilbert, Ariz. Marcus Dortch, PharmD, is senior director of clinical pharmacy services at HealthTrust.
Health policy wonks have been sounding the alarm for decades that the American health care system won’t get better until it is less fragmented and better coordinated. Vulnerable patients stay sick because the system is so hard to use, so care coordinators are in great demand to ensure the chronically ill get to the doctor, take their meds, and report new symptoms. So now that everyone has seen the light and unleashed legions of care coordinators to check up on patients, it would be unseemly to complain about this welcome development. Wouldn’t it?

Not necessarily. Clinicians and caregivers who focus on high-risk patients report that the enthusiasm has gone a little far. They increasingly find their care coordinators bumping into others assigned by another practice, agency, or organization. Or, worse yet, they don’t even know about their counterparts until a patient has been given conflicting advice by one of them. The potential for mixed signals, confused patients, and wasted time and money is real.

“Sometimes [our clients] will have multiple case managers,” notes Maria Raven, MD, an associate professor of emergency medicine at the University of California–San Francisco, who oversees a care management program for San Francisco Health Plan, which provides city-sponsored coverage to low-income residents. “They may not know about each other and there’s no formalized way for them to coordinate. Sometimes they want to [work together] and sometimes they don’t.”

Health care, an industry particularly vulnerable to the promise of silver-bullet solutions, has embraced care coordination in a big way. And it only makes sense that high-risk patients—those with severe, chronic, or multiple conditions, and maybe some economic and social issues as well—shouldn’t just be chucked out the door when they are discharged. Someone should check up on them, make sure they are healing, taking their meds, getting to their follow-up medical appointments.

The question is, who? The hospital, fearing a penalty if the patient ends up readmitted within the month, assigns a care manager. The ACO, whose very existence is based on care coordination, is a natural for this job. The insurance company wants a hand in because their bottom line is at stake. The primary care doctor’s office has been told it’s their ultimate responsibility that the patient stays well, so there’s pressure to follow up. The specialist who performed a procedure in the hospital may get dinged financially by a poor outcome, so it’s in her interest to track the case. There are probably medications involved, so the pharmacy benefit manager wants to be sure drugs are used cost effectively. The pharmacy is probably by now associated with an insurer or provider in some way, so they’ll give a jingle to be sure the prescription gets filled.

Lost count yet? Some patients may enjoy—some may even benefit from—all the attention. Or they may be like the recently discharged patients the Advisory Board followed; they had received, on average, 9.5 calls from care managers in the week after their hospitalization. Most got annoyed and ignored all but the primary care doctor’s office.
“Everyone is kind of fumbling over each other, particularly because the demarcation lines about who is responsible for the patient at what time are undefined,” acknowledges François de Brantes, director of the Center for Payment Innovation at the Altarum Institute. But he sees the fumbling as temporary and the surge in care coordination as an indication that the system is, at long last, responding to patient needs. “It’s really a positive sign because it means the delivery system is adapting and adapting in the right way.”

Some of this coordination comes from a sincere intention to do the right thing. It is also fueled by payment models that are handing financial responsibility for a patient’s health to more parties. Insurers—they have always had a financial motivation for coordinating care. Now so does everyone else—primary care physicians, oncologists, ACOs—taking on financial risk in the form of bundle payments, shared savings, or pay-for-performance of one kind or another. Even drug manufacturers are being pulled into the risk-taking business by signing contracts that offer refunds if their products don’t perform.

Primary care doctors tend to find the scrum irritating because they have the most to lose and the least time and resources to deal with it. “If you have a care coordinator; the task was being carried out by others, such as insurers, who did not check in with her on protocols. “I might tell my congestive heart failure patient to call my office if they gain five pounds overnight,” she says. “An insurer might tell them if you gain two pounds a day for three days call your primary care doctor.”

When multiple players get involved, it just furthers fragmentation of care and invites the potential for miscommunication and patient harm, says Lillie. Her least favorite intrusion is from pharmacy benefit managers, who may send a letter to the patient questioning the doctor’s medication choice without consulting with her. “It’s not coordination to get a fax from the pharmacy benefit person who looked at the care out of context,” she says.

Raven, at San Francisco Health Plan, sees the multiple care managers and coordinators as meaning well, but potentially causing confusion. Because her program invests a lot of time in tracking down frequent ED visitors, who often have thorny and time-consuming housing and transportation problems, SF Health Plan care coordinators are trained to consider themselves the “accountable person” and take the lead in figuring out who else has been in touch with the client.

The care coordinators with Camden Coalition in New Jersey, an early leader in innovating population health for vulnerable populations, say part of the confusion happens when there is overlapping coverage of patients by multiple players whose lists don’t jibe. “They’re getting a list based off of different algorithms, and it can be overwhelming to figure out which of those patients overlap,” says Kelly Craig, chief strategy and information officer for the coalition.

As part of a program to reach super-utilizers of medical services, the coalition sponsored a monthly meeting with partner organizations across the city, carrying out root-cause analyses of each patient and identifying any overlap among their services. But that meeting has become untenable as the program has grown and more participating organizations are using population-health methods. “Now there are so many more entities, [the regular meeting] has become less effective and it’s harder to get everyone in the room.”

The lack of coordination, she says, “has definitely gotten worse over time.”

Some of the overlap is from well-meaning not-for-profits offering solutions to social ills, but a lot of it is fueled by organizations newly incentivized to save money on high-utilizing patients. Asking an organization whose financial viability may be decided by its care coordination program to back off and let others take the lead may be a hard sell.

**The intrusion that most annoys**

family practice physician Lynne Lillie, MD, is when a PBM sends a patient a letter questioning a doctor’s decision without first talking with the doctor.

pharmacy benefit manager and hospital case manager and an insurance plan care manager, you have three different care managers involved,” says Lynne Lillie, MD, a family physician in Rochester, Minn., who sits on the board of the American Academy of Family Physicians. “It’s hard to recognize any improved outcome from their involvement.”

**PBM:s Personae non grata**

Lillie has worked in settings where care management is coordinated well and in those where it’s not.

In her well-organized ambulatory care practice, she can go down the hall and ask a care coordinator to help the patient in her office with logistics of managing his illness. “We have the ability to send a community health worker to the home and make assessments and check whether there is food in the fridge,” Lillie says.

On the other hand, she used to work in a small town where the practice couldn’t afford an in-house
That kind of friction can appear when payment models overlap, notes de Brantes. He offers a scenario: An ACO shares a patient with a partnering specialty practice—oncologists, for instance—who are working under a separate specialty payment model. They are both trying to provide efficient care for the same patient. Who gets precedence?

“This is something we’re just starting to work on with a couple of the large national payers,” de Brantes says. The solution, he says, may be in writing contract language with payers that is explicit about which overlapping organization has responsibility for plan members when they get specialty care covered by another contract.

HIEs … if only
De Brantes believes another answer lies in health information exchanges providing a central repository of patient data. “It starts by having an unfettered flow of clinical data between all the providers that touch a patient,” he says. Easy, secure electronic messaging among providers would also help.

Those seemingly simple goals have been elusive in most health care markets because of conflicting software and competing providers who lack incentives to share patient information. Recognizing those challenges, the Camden Coalition has invested in legal and technical staff to iron out information-sharing difficulties and privacy concerns. Still, says Craig, it’s frustrating.

“Even when we make a concerted effort to make the information available online, people don’t use it,” she says. “It’s only as helpful as someone’s willingness to use that system. Folks may not have time or the right workflows to access that, and then you’re not improving quality and duplication of effort happens.”

De Brantes’s organization, when pulled in to get a population-health effort off the ground, often finds itself working with health care organizations and social service agencies that are serving the same patients but have utterly different information systems. Altarum will manually set up an electronic registry that lets the systems share information.

Integrated delivery systems that act as provider and payer may have a head start on coordination because

---

**Confusion often happens**
when there is overlapping coverage of patients by multiple players whose lists don’t jibe, says Kelly Craig of the Camden Coalition.

---

**But sometimes, there’s a lack of a needed care coordinator**

A Commonwealth Fund survey of 1,805 “high-need” patients found that many (43%) have needs that a care coordinator might help with but they didn’t have a care coordinator. Others (15%) who did have a coordinator considered the person uninformed. Most of the high-need patients surveyed had multiple complex chronic conditions, some were under age 65 and disabled, and a minority were frail elderly.

The survey also found:
- 37% of high-need patients often feel socially isolated or lonely
- 62% are stressed or worried about material hardships, such as paying for housing, utilities, or nutritious meals (compared with 32% of other adults)
- 59% are somewhat or very concerned about being a burden to family or friends
- 44% delayed care in the past year because of an access problem, such as lack of transportation, limited office hours, or inability to get an appointment quickly enough
- 35% report it is easy to get medical care after hours without going to the ER (compared with 53% of other adults)

---

*Source: Commonwealth Fund, “How High-Need Patients Experience Health Care in the United States,” December 2016*
care delivery and money flows are already joined at the hip in information systems. “We can align far better than other organizations with the use of a technology platform that tracks the roles and tasks of each provider along the care continuum,” William Shrank, MD, medical director of UPMC’s health plan, wrote in response to questions from MANAGED CARE. “We place care manager ‘quarterbacks’ within communities who get to know the patients they manage personally.”

A team sport
So who should coordinate the coordinators? Not surprisingly, family physicians think they should be at the center of the spokes. And many in population health agree that if the patient has a primary care doctor—particularly one who runs a medical home-style practice that is prepared to coordinate care—medical decision making should be run through that practice.

“Collaboration with insurance providers can be a really powerful solution” for tracking high-needs patients, says Natasha Dravid, director of the Camden Coalition’s redesign initiatives.

But what about the social determinants of health—the welter of transportation, housing, and family problems that can affect health, directly and indirectly? Isn’t it too much to expect a primary care office to take responsibility for that, too?

Primary care practices don’t need to be afraid to take on the social determinants, argues de Brantes, particularly because emerging payment models will require it. But they can outsource the work. “You have to feel comfortable as a primary care physician to delegate social needs to organizations that can take the relay,” he says. Primary care practices need to see themselves as being part of the community, not just the medical system, and be willing to lean on not-for-profits that can help their patients with problems that affect health but haven’t been traditionally seen as the province of health care providers.

But is this all too pie in the sky? It will depend on the relationship between health care providers and their social service partners, notes Melinda Abrams, vice president of delivery system reform for the Commonwealth Fund. “It requires a lot of trust because I’m relying on the social service provider to meet my financial bottom line,” she says. But relationships are what all of value-based care relies upon, she says. “Trusting relationships between patient and practice, health care organization and social service provider, payer and provider … this needs to be a team sport.”

Another likely central coordinator is the insurer, because each patient is likely to have just one at a time. The insurer can gather information through claims from a variety of providers and so has a bird’s-eye view of the whole care landscape. The problem, of course, is that providers and patients are wary of insurers and their cost considerations getting too involved in health care decisions.

The Camden Coalition works closely with its insurer partners to share information and track high-needs patients, says Natasha Dravid, director of the organization’s clinical redesign initiatives. “Collaboration with insurance providers can be a really powerful solution,” Dravid says.

De Brantes believes health plans should be stepping forward to help make sense of it all. “It is incumbent on the health plan to say, ‘You guys are sharing the same patient. We get it, you have an incentive to care for the patient, but you all should be talking to each other so you don’t end up with three different people calling this poor plan member.’”

Another option is to add a layer of coordination such as the one developed by the Advisory Board that it calls a population health services organization (PHSO). The PHSO, usually based within a provider organization, takes the lead on care coordination and offers all the care coordinators assigned to the patient a common care plan.

Others are sanguine and figure it will work itself out as everyone gets used to new relationships and workflows that population health brings with it. “We are in the middle of this evolutionary process to better coordinate care,” says Abrams at the Commonwealth Fund. “It is a massive paradigm shift and we need to give it time.”

Jan Greene is a veteran health care journalist based in Northern California. Her work has appeared in the Los Angeles Times, Health magazine, Hospitals & Health Networks, and other publications.

CALL FOR PAPERS
MANAGED CARE is seeking article submissions. We welcome a wide variety of manuscripts, including drug class reviews, disease state management reviews, pharmacoeconomic analyses, strategies for coping with medication errors, and outcomes research. Interested? Write to our managing editor, Frank Diamond, at fdiamond@medimedia.com.
Imagine our body as a symphony and our organs as the performers and instruments. Each instrument plays a key role in the entire musical experience as each individual sound from each instrument comes into play at precisely the right time and at the right frequency and beat. Each performer listens for the other instruments to queue their contribution.

The kidneys may not be the concertmasters of the physiological orchestra, but they are certainly major instruments. They do much more than simply filter blood. Healthy, well-functioning kidneys are inextricably connected with the parathyroid gland, bones, and cardiovascular system. The structure and function of the kidneys can be measured with simple imaging, blood, and urine tests. As the kidneys lose function, primarily due to hypertension and diabetes, the diagnosis of chronic kidney disease (CKD) can be made from these tests. If CKD worsens to the point that life is threatened, it becomes end stage renal disease (ESRD). Dialysis or kidney transplantation are the only treatments for ESRD. Currently, about 460,000 Americans with ESRD are receiving dialysis. As the prevalence of diabetes—especially type 2 diabetes—continues to rise, the number of Americans with CKD or ESRD needing dialysis is also expected to increase.

The rapid increase in the incidence and prevalence of diabetes, CKD, and ESRD has emerged as a large (and potentially lucrative) target for pharmaceutical companies. They are plowing millions of research-and-development dollars into elucidating the intricacies of the renal system and its pathology.

Step-by-step

CKD and ESRD also go hand in hand with a secondary condition called mineral and bone metabolism disorder, or CKD–MBD. CKD–MBD is a triad of biochemical, bone, and vascular abnormalities: abnormal serum levels of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH); abnormal bone turnover and mineralization, which affect growth and strength; and calcification of soft tissue, especially blood vessels (particularly in the heart).

As CKD–MBD progresses, the severity and number of these abnormalities generally increase to the point that normal homeostatic processes cannot keep up and problems ensue. The processes involved are so complex that the understanding of the sequence in which they occur is incomplete and the explanations often speculative.

But in broad brushstrokes, as the nephrons of the kidney lose function, calcium levels start to drop, in part because of a reduction in gastrointestinal absorption. Phosphate rises as the kidney decreases secretion, which, in turn, stimulates the parathyroid gland to produce more PTH to push the kidney into trying to rid
calcium and phosphate levels. In both studies, a significantly higher proportion of patients treated with Parsabiv achieved reductions in PTH levels as well as calcium and phosphate.

Better adherence, better control of CKD–MBD caused by secondary hyperparathyroidism—who can argue with that? Assuming the cost of Parsabiv and cinacalcet is about the same, it is likely to be a wash—at least initially.

But the patents for cinacalcet end in mid-2018. The generic products will likely—if not right away, eventually—be much lower in cost than for Parsabiv.

Although CMS sets reimbursement for dialysis patients covered by Medicare, commercial plans pay a significant part of the total cost of dialysis. Dialysis centers have historically maintained enormous pricing power over health plans, often charging multiples of the average sales price (ASP) for dialysis drugs. Parsabiv, because it will be administered as part of dialysis, will probably be priced at a huge markup for commercial plans.

No head-to-head trials were done between these two Amgen products. What’s more, endpoints were tweaked to be just dissimilar enough to make direct comparison of the outcomes for cinacalcet and Parsabiv virtually impossible. My spidey sense analysis of the labels for both drugs suggests to me that the results are similar. But so far, my spidey sense does not constitute proof.

Major markup
Nephrologists will need to decide what is best. The calcimimetics are expensive. The standard dose of orally branded cinacalcet starts at about $900 per month retail. If the maximum dose is needed, the cost can triple, so the annual bill is often more than $30,000. Payers are hoping that the generics will be priced much lower.

Meanwhile, facility-infused drugs are likely to be marked up by multiples of the ASP.

On the bright side, the approval of Parsabiv and the cinacalcet generics present opportunities for managing this category of drugs in a smart, cost-effective way.

But Parsabiv is also an example of how lack of head-to-head trials, site-of-care differences, and minor adjustments can help pharmaceutical companies maintain sale of high-priced drugs even with generic competition. Health plans are well advised to keep a diligent watch.
Innovative Care Model to Improve Clinical Quality and Safety of Transitional Care: Early Outcomes
Brooke Roeper, MSPH, MS; Eric Beck, DO, MPH, FACEP; Daniel Castillo, MD, MBA; J. Brent Myers, MD, MPH; Brandy Sparkman, RN, BSN; Jonathan Cox, MHS; Scott Bourn, PhD, RN, EMT-P*
All the authors are employees of Evolution Health, Dallas, Texas

ABSTRACT
Background: The high rate of 30-day hospital readmissions among Medicare patients highlights a glaring care gap in the treatment of elderly patients. To improve quality of care, increase patient safety, and reduce the associated costs of these readmissions, transitional care programs are being implemented to facilitate continuity of care from hospital to home with the goal of preventing return visits to the hospital.

Intervention: Evolution Health, a provider of mobile integrated health care, evaluated transitional care best practices, and developed and implemented an evidence-based transition of care (TOC) program to effectively reduce 30-day readmission rates among high-risk Medicare patients.

Evaluation: Data were collected and analyzed to assess the effectiveness of the TOC program among Medicare patients discharged from a five-hospital health system between Dec. 1, 2014, and Oct. 31, 2016. The 30-day program featured an interprofessional mobile integrated team, overseen by a medical command center, providing 24/7/365 support to Medicare patients following their hospital discharge. Post-intervention readmission rates were calculated for patients discharged with one of five ACA Hospital Readmissions Reduction Program (HRRP 5) reportable discharge diagnoses: total hip or knee replacement, myocardial infarction, heart failure, pneumonia, or chronic obstructive pulmonary disease.

Results: For the five discharge diagnoses collectively, 30-day readmission rates for participants in the TOC program (11.0%) were substantially lower than those reported for the general Medicare population (18.3%).

Conclusion: Preliminary outcomes suggest that Evolution Health’s TOC program was effective in improving clinical outcomes, thereby reducing 30-day readmission rates for Medicare patients discharged with an ACA HRRP reportable discharge diagnosis.

INTRODUCTION
The U.S. health care system is suffering from what can be called “the revolving door syndrome” (Goodman 2013), where one in five elderly patients returns to the hospital within 30 days of leaving (Leppin 2014). These readmissions are a common and costly occurrence among Medicare beneficiaries, with the 30-day hospital readmission rate among Medicare fee-for-service beneficiaries averaging 17.5% in 2013 (HHS 2014). Unplanned readmissions cost Medicare $26 billion annually, with an estimated $17 billion spent on potentially avoidable readmissions (Brennan 2014). High rates of unplanned readmissions suggest substantial quality of care that results in unnecessary expenses. For this reason, reducing unnecessary rehospitalizations among Medicare beneficiaries has become a high priority for both clinical quality and cost reasons.

The Patient Protection and Affordable Care Act instituted the Hospital Readmissions Reduction Program, which holds hospitals accountable for unnecessary rehospitalizations by imposing financial penalties on hospitals with greater than expected readmission rates. According to a Kaiser Health News analysis, the federal government's readmission penalties on hospitals will total more than half a billion dollars in payments in the 2017 fiscal year (Oct. 1, 2016–Sept. 30, 2017) (Rau 2016). The average penalty was 0.73% of each Medicare payment.

Despite uncertainty regarding the survival of some ACA programs, those aimed at reducing waste in the health care system are likely to remain. Thus, the change in Medicare’s approach to preventable rehospitalizations has motivated payers and providers to seek new solutions for managing patients following discharge.

The lack of postacute transitional care and the inability of patients to receive help from their primary care physicians outside of traditional business hours impede the timely delivery of care to elderly patients. Recognition of this care gap has driven the development and implementation of transitional care models, such as Project RED (Jack 2009), the Transitional Care Model (Naylor 2004), and Care Transitions Intervention (Coleman 2006).

Evolution Health adapted and combined current transitional care best practices (Boutwell 2009a, Boutwell 2009b) and evidence-based care plans (Rutherford 2013, Feltner 2014) to create a care program

Acronyms and initialisms
HCO=Health Care Organization
HRRP=Hospital Readmissions Reduction Program
MCC=Medical command center
MIT=Mobile integrated team
TOC=Transition of care
that seeks to provide appropriate care for high-risk elderly patients in their own homes.

**TOC program**
This TOC program builds upon the previously described mobile integrated health care practice (MIHP) strategy (Beck 2013, Castillo 2016), a model designed to serve a range of patients in an outpatient setting by providing 24/7 needs-based at-home care. For this TOC program, the model was refined to successfully deliver transitional care to elderly, high-risk patients.

**Medical command center**
The TOC program utilizes an interprofessional mobile integrated team (MIT), supported by a medical command center (MCC). The MCC is a comprehensive, integrated, 24/7 coordinating resource for managing the health of a designated patient population. The MCC serves as a communication hub that is equipped with clinical expertise and the ability to provide need-matched, timely resource allocation for both planned and unplanned care. The interprofessional team comprises nurses, clinical pharmacists, social workers, and nonclinical support staff. A physician medical director provides clinical oversight around the clock.

The MCC is supported by a clinical triage and care management platform with predictive capabilities to enhance the coordination of longitudinal patient care and postacute transitional care for high-risk individuals. A computer-assisted dispatch program optimizes resources for planned care (e.g., avoiding acute visits via follow-up care and medical treatment for elderly patients with congestive heart failure) and the rapid deployment of an MIT member directly to the home of patients requiring urgent, emergent, or unplanned care.

A telephone system with automated call distribution facilitates the efficient routing of incoming calls and enhanced caller experience (i.e., ability to manage the patient’s problem during the call rather than leaving a message for the physician).

Built upon established experience utilizing telemedicine and telehealth monitoring, the MCC is designed to communicate relevant patient information to community care team members, which include primary care providers, case managers, and home health agencies.

The MCC enables streamlined communication among the patient care team and uninterrupted, around-the-clock access to a physician-led, interprofessional MIT. In addition, the MCC triages and escalates unplanned, urgent, and emergent patient issues and manages patients safely in their homes.

**Mobile integrated team**
Supported by the MCC, the physician-led MIT consists of field-based nurses (licensed visiting nurses or registered nurses); emergency medical technicians or paramedics; licensed social workers; clinical pharmacists; and prescribing providers (physician, advanced practice nurse, or physician assistant). A medical director who is a physician oversees the team and works under the oversight of a physician medical director.

At any time, the team can be deployed to the patient’s home when acute, urgent, or time-sensitive care is required, thereby preventing unnecessary and inappropriate emergency department visits or hospital admissions.

Protocol-driven escalation procedures guide the nonprescribing team’s response to unplanned, urgent, and emergent medical situations, and may include in-person or virtual involvement of an physician, advanced practice nurse, or a physician assistant.

**Application in an HCO setting**
The health care organization (HCO)* is a network of five acute-care hospitals that provide care for patients throughout a large metropolitan area of more than 2 million people. The hospitals are accredited by the Joint Commission and offer a comprehensive range of health care services.

Once patients are enrolled in the 30-day TOC program, they receive a predischarge visit with an RN to introduce the care team, establish rapport with the patient, ascertain the presence of any unusual issues that may affect the postacute care transition, obtain consent for the program, and plan for the initial postdischarge contact. Utilizing a registered nurse with a high level of expertise at this stage differentiates this TOC program from other transitional care models. The predischarge visit is followed within 24 hours by an initial in-home visit by an advanced practice nurse or physician assistant. During this visit, the clinician:

- Assesses cultural and literacy levels
- Assesses patient activation level
- Obtains a medical history
- Evaluates home safety
- Reviews discharge instructions
- Obtains vital signs and height/weight/body mass index
- Performs physical examination and functional assessment
- Reconciles medications
- Manages acute issues and identifies potential care gaps
- Initiates the patient’s care plan
- Provides patient education and health coaching for self-management, including a discussion of contingency plans for changes in status
- Provides a plan for upcoming calls or in-home visits and assists with scheduling primary care provider appointments

* Name anonymized for this publication
• Provides MCC contact information and reinforces the importance of contacting the MCC with all health concerns.

Over the course of the 30-day program, participants receive additional in-home visits and weekly telephone calls as determined by their plan of care developed during the predischarge and initial in-home visits. During these visits and calls, the interprofessional team members review the patient’s interim health status, reconcile medications, provide any necessary health coaching and patient education, discuss contingency plans for any change in health status, and plan for upcoming calls or scheduled in-home visits.

Evaluation method
Participants in this study were Medicare fee-for-service beneficiaries discharged from an HCO hospital between Dec. 1, 2014, and Oct. 31, 2016, with one of five ACA Hospital Readmissions Reduction Program (HRRP 5) diagnoses: hip or knee replacement (hip/knee), myocardial infarction (AMI), heart failure (CHF), pneumonia (PNA), and chronic obstructive pulmonary disease (COPD). Prospective participants were selected and referred by the HCO, and enrollment was voluntary. Patients discharged to group homes or long-term care facilities were excluded.

The primary outcome measure was the rate of readmission at 30 days after discharge from the index hospitalization. The HRRP 5 readmission rates were measured individually, and a core diagnoses aggregate readmission rate was calculated by combining the data from these five groups.

RESULTS
From Dec. 1, 2014, through Oct. 31, 2016, 684 Medicare fee-for-service patients with one of the HRRP 5 diagnoses were referred by the HCO and enrolled in Evolution Health’s TOC program. Of these patients, 75 were rehospitalized within 30 days of hospital discharge (11.0%).

Pre-intervention and direct comparison data were not made available by the HCO. However, Medicare fee-for-service enrollment and claims data are available from the CMS Hospital Compare (CMS 2017). A review of 30-day unplanned readmission data for all patients discharged from any of the HCO’s five hospitals with HRRP 5 from July 1, 2012, through June 30, 2015, revealed a collective rehospitalization rate of 18.3% (1,072 of 5,855).

The table below contains descriptive summary statistics of the total number of patients, the number of readmissions, and the readmission rates for TOC program patients and for the general population of Medicare fee-for-service patients discharged from the HCO hospitals with one of the five diagnoses. Although a direct comparison cannot be drawn, the 30-day readmission rates for the five diagnoses were lower for program participants than those for nonparticipants whether viewed collectively or individually.

DISCUSSION
The current emphasis on value-based health care and hospital accountability has heightened the health system’s interest in promoting high-quality, safe, and cost-effective health care. Evolution Health developed and implemented its TOC program to address the quality of care and safety problems during postacute transitional care.

Early outcomes suggest the program may be an effective means for reducing 30-day readmission rates among Medicare fee-for-service pa-

<table>
<thead>
<tr>
<th>Core diagnosis</th>
<th>TOC Program</th>
<th>General Medicare patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Readmits</td>
</tr>
<tr>
<td>Hip/knee</td>
<td>241</td>
<td>10</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>178</td>
<td>29</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>107</td>
<td>10</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>102</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>684</td>
<td>75</td>
</tr>
</tbody>
</table>
patients discharged from the HCO with an ACA HRRP-reportable discharge diagnosis, particularly those with congestive heart failure (16.3% readmission rate vs. 24.5% for the general Medicare population) and pneumonia (9.3% readmission rate vs. 18.2% for the general Medicare population).

Here are some of the actions taken by the physician-led, interdisciplinary teams of this TOC program that may have contributed to lower readmission rates:

1) Laying groundwork for the hospital/home transition by sending a registered nurse into the hospital prior to discharge to develop the patient’s care plan;

2) Reviewing medications for therapeutic duplications, drug-drug interactions, and other medication-related issues that could have had a negative impact on patient safety;

3) Getting a prescribing provider into the patient’s home within 24 hours of discharge to evaluate home safety, initiate the care plan, and empower the patient by providing education and health coaching;

4) Providing around-the-clock support by triaging patients when they call the MCC for unplanned care, and then rapidly deploying the appropriate member of the care team to the patient’s home; and

5) Coordinating care between the patient’s primary care physician, specialists, home health agency, and case manager.

**Limitations**

Participants were selected from a general Medicare fee-for-service population and referred by the HCO. Patients discharged to long-term care or group homes were not included. Pre-intervention data for this population were not made available to Evolution Health, thus direct comparisons between matched cohorts were not possible. Conclusions were drawn by comparing the participant group with the general population of Medicare patients discharged from HCO facilities with one of the HRRP 5 diagnoses (i.e., the comparison group for a given time frame would include the subset of higher-risk patients who were excluded from participation in the program). Evolution Health is working with the HCO and other providers to obtain comparison data from matched cohorts for future analyses.

**CONCLUSION**

Early outcomes indicate that the Evolution Health TOC program may be effective in closing the post-acute transitional care gap, thereby reducing preventable readmissions and improving quality outcomes for a participant group of Medicare beneficiaries. Additional research is needed to determine the proportional contributions of each component of this TOC model and to better understand the relationship between reductions in readmission and actual cost savings.

**References**


**Correspondence:**

Brooke Roeper
Manager of Outcomes and Epidemiology
Evolution Health
13737 Noel Road, Suite 120
Dallas, TX 75240
(214) 470-7333
brooke.roeper@ehc.net

**Acknowledgements:** Janice L. Clarke, RN, and Alexis Skoufalos, EdD, from the Jefferson College of Population Health in Philadelphia, provided editorial assistance.
Send Us Your Nominees!

We are putting together a list of the 10 most important people in managed care for our August 2017 issue.

Who belongs on our Mount Rushmore (plus six) list? Who has clout? Who has influence?

Who are original thinkers about the ways in which American health care could be delivered and paid for?

And who has come up with the innovations that are working—the ideas and programs shaping the future of health care?

You tell us.

Please write Frank Diamond, MANAGED CARE’s managing editor, at fdiamond@medimedia.com

ALSO

We are interested in your insights and ideas for our September issue on how doctors get paid and our October issue on autoimmune disease.
Professional Networking for Medical Directors by Medical Directors

The first and only site that offers Medical Directors a verified, secure, closed-loop environment for peer-to-peer interaction.

The Medical Directors Forum offers a comprehensive resource library, discussion groups, calendar postings and alerts—giving Medical Directors the opportunity to network and share ideas on a robust site.

JOIN FREE NOW BY REGISTERING AT:

www.medicaldirectorsforum.com
New treatments for rare or “niche” diseases have the potential to positively impact the lives of millions of patients. But they also bring new challenges for health plans struggling to manage rising diagnostic and treatment costs. The rapid increase in pharmacy costs is an especially difficult problem. Although there is no “silver bullet” to these challenges, two approaches can help assure better care for patients with niche diseases as well as manage costs.

First, providers should make sure that prescribed therapies are titrated according to accepted clinical guidelines.

Second, when clinically appropriate, as much care as possible should be provided in the patient’s home. Consider as an example the management of chronic inflammatory demyelinating polyneuropathy (CIDP), a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. CIDP is closely related to Guillain-Barre syndrome, and some experts believe that it is the chronic form of the syndrome.

Treatment of CIDP often includes intravenous immunoglobulin (IVIG), which costs thousands of dollars per dose. Health plans should evaluate their infusion networks and specialty pharmacy vendors to ensure use of standardized approaches to IVIG treatment. The quality of IVIG treatment of patients with CIDP can be improved by using a protocol-driven approach that uses clinical measurements to determine appropriate dosing. In many cases, patients are started on IVIG and dose adjustments that would benefit the patient are made too late. What’s more, dose adjustments are sometimes made without careful consideration of objective data to guide dose escalation or reduction.

Successful new clinical programs use dosing protocols for IVIG based on just this kind of objective measurement. It is called the inflammatory neuropathy cause and treatment (INCAT) score.

A recent study published in the *Annals of Neurology* demonstrated that patients treated in a way that follows dosing protocols were more likely to have stable or improved INCAT scores compared with patients where physicians chose not to follow the protocol-based recommendation.

Moreover, this approach may reduce costs by more quickly identifying patients who are not responding to therapy, so the dose can be changed or the patient switched to medications that are less expensive than IVIG.

Another approach to reducing costs for treatment of CIDP is to move IVIG dosing from infusion centers to patient homes. Home infusions can be between 30% and 40% less expensive than treatment in an infusion center.

Patients are often not aware that home IVIG infusion is a safe—and less expensive—alternative. And in this era of rising copayments and coinsurance and high-deductible plans, patients as well as insurers benefit from the cost savings.

There’s no question that the advent of new treatments for niche illnesses is improving the quality of life and providing hope for patients with rare diseases. Previously, there were few, if any, treatments.

But health plan leaders can’t be caught flat-footed. They need to keep pace with the introduction of these new treatments and be ready with strategies that address patient needs and manage costs. Using objective clinical data to guide dosing and working to redirect care—when appropriate—to a patient’s home is a place to start.

*Your turn:* Post your response at medicaldirectorsforum.com/curbsideConsult
ViiV Healthcare can help

As the only company solely focused on HIV, ViiV Healthcare can help you better understand and meet the needs of your members living with HIV.

ViiV Healthcare is a global specialist HIV company dedicated to delivering advances in treatment and care for people living with HIV. The company’s aim is to take a deeper and broader interest in HIV/AIDS than any company has done before, and take a novel approach to delivering new and effective HIV medicines, as well as supporting communities affected by HIV.

Connect with us at
www.viivhealthcare.com